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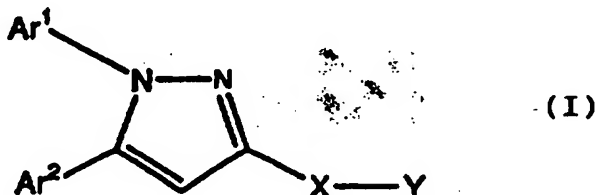
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<p>(21) International Application Number: PCT/JP95/02250 (22) International Filing Date: 6 November 1995 (06.11.95)  (30) Priority Data: 6/274067 8 November 1994 (08.11.94) JP 6/280705 15 November 1994 (15.11.94) JP 7/48760 8 March 1995 (08.03.95) JP  (71) Applicant (for all designated States except US): EISAI CO., LTD. [JP/JP]; 6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo 112 (JP).  (72) Inventors; and (75) Inventors/Applicants (for US only): NUMATA, Hirotochi [JP/JP]; 13-5, Ottominami 3-chome, Tsuchiura-shi, Ibaraki 300 (JP). OKAMOTO, Yasushi [JP/JP]; 4-15, Kinunodai 6-chome, Yawaramura, Tsukuba-gun, Ibaraki 300-24 (JP). SHINODA, Masanobu [JP/JP]; Arkflat 107, 25-9, Matsushiro 2-chome, Tsukuba-shi, Ibaraki 305 (JP). KOBAYASHI, Naoki [JP/US]; One Watermill Place 307, Arlington, MA (US). MIYAZAWA, Shuhei [JP/JP]; 39-26, Matsugaoka 2-chome, Moriyamachi, Kitasouma-gun, Ibaraki 302-01 (JP). KAWAHARA, Tetsuya [JP/JP];</p>		<p>Domyuru Tsukuba 303, 17-4, Agatsuma 4-chome, Tsukuba-shi, Ibaraki 305 (JP). SHIROTA, Hiroshi [JP/JP]; 1077-41, Yatabe, Tsukuba-shi, Ibaraki 305 (JP). NAGAKURA, Naoki [JP/JP]; Tsukubanedainiryo 307, 9-7, Inarimae, Tsukuba-shi, Ibaraki 305 (JP). HORIZOE, Tatsuo [JP/JP]; Mezon Gakuen 207, 23-5, Amakubo 2-chome, Tsukuba-shi, Ibaraki 305 (JP). ABE, Shinya [JP/JP]; 1083-44, Onabakecho, Ushiku-shi, Ibaraki 300-12 (JP). KOBAYASHI, Seiichi [JP/JP]; 10-26, Nakatakatsu 2-chome, Tsuchiura-shi, Ibaraki 300 (JP). YAMANAKA, Takashi [JP/JP]; 725-25, Shimohirooka, Tsukuba-shi, Ibaraki 305 (JP).  (74) Agents: FURUYA, Kaoru et al.; Nihonbashi TM Building, 1-8-11, Nihonbashi-Horidomecho, Chuo-ku, Tokyo 103 (JP).  (81) Designated States: AU, CA, CN, FI, HU, JP, KR, MX, NO, NZ, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report.</p>

(54) Title: PYRAZOLE DERIVATIVES EXHIBITING ANTI-INFLAMMATORY AND ANALGESIC EFFECTS

(57) Abstract

Pyrazole derivatives represented by formula (I) and physiologically acceptable salts thereof can suppress the production of both of prostaglandins and leukotrienes simultaneously, and, therefore, exhibit anti-inflammatory and analgesic effects.



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## DESCRIPTION

## PYRAZOLE DERIVATIVES EXHIBITING ANTI-INFLAMMATORY AND ANALGESIC EFFECTS

## Background of the Invention

## Field of the Invention

The present invention relates to pyrazole derivatives and medicaments containing the pyrazole derivatives.

## Description of the Related Art

As anti-inflammatory/analgesic agents, there have been widely employed nonsteroidal anti-inflammatory agents such as acetylsalicylic acid, indomethacin, ibuprofen and diclofenac sodium. Such existing anti-inflammatory agents exert their efficacies by inhibiting the cyclooxygenase series in the arachidonate cascade to thereby suppress the production of prostaglandins.

The clinical efficacies of anti-inflammatory/analgesic agents reside in the amelioration of subjective symptoms, as represented by the analgesic effect. However, it is thought that these agents are not efficacious against tissue lesions or the progression of diseases accompanying changes into chronic inflammation.

On the other hand, it has been clarified that leukotrienes (LTs), which are the metabolites in the 5-lipoxygenase series in the arachidonate cascade, have physiological effects differing from those of prostaglandins (PGs). Because of its having a potent leukocyte migration activity, in particular,  $LTB_4$  seemingly participates in the progression of inflammation via the accumulation of leukocytes in the inflammatory site and thus plays an important role in the subsequent tissue lesion caused by cytokine or the like. Actually it has been reported that patients with rheumatoid arthritis clinically show high synovial  $LTB_4$  level, which suggests that  $LTB_4$  would participate in the pathology of rheumatoid. It has been also reported that  $LTC_4$  and  $LTD_4$  show potent effects of enhancing vascular permeability and, in the coexistence of  $PGE_2$ , synergistically enhance the permeability. However, there has been clinically known no nonsteroidal anti-inflammatory agent capable of suppressing the production of both of PGs and LTs simultaneously.

#### Disclosure of the Invention

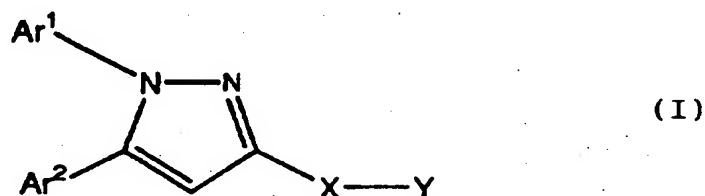
##### Summary of the Invention

The present inventors have found that the



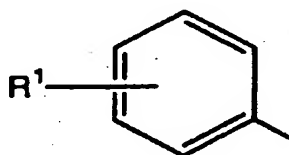
specific pyrazole derivatives would simultaneously suppress the production of PGs and LTs, thus completing the present invention.

Namely, the present invention provides a pyrazole derivative represented by the following formula (I) or a physiologically acceptable salt thereof:



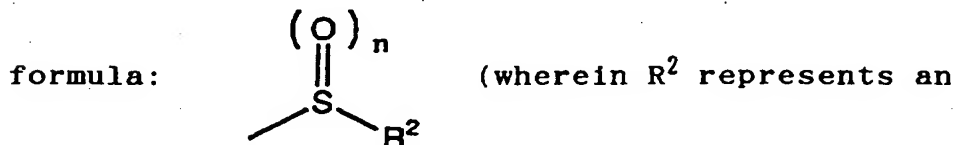
wherein Ar<sup>1</sup> and Ar<sup>2</sup> may be the same or different from each other and each represents an optionally substituted heterocyclic group or a group represented

by formula:



[wherein R<sup>1</sup>

represents a hydrogen atom, an optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, a halogen atom or a group represented by

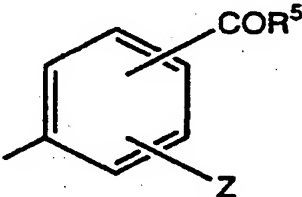


optionally halogenated lower alkyl group or an optionally substituted amino group; and n represents an integer of 0, 1 or 2)];

X represents a group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  may be the same or different from each other and each represents a hydrogen atom, a hydroxyl group, an optionally halogenated lower alkoxy group, a halogen atom or an optionally protected carboxyl group, or  $CR^3R^4$  may form a five- or six-membered ring having a carbon atom(s) optionally together with an oxygen atom(s) as the ring-constituting atoms); or a group represented by formula:  $>C=O$ ; and

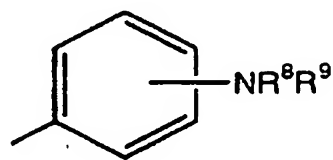
Y represents an optionally substituted aryl group, an optionally substituted furyl group, an optionally substituted thienyl group, an optionally substituted pyridyl group, an optionally substituted thiazolyl group, an optionally substituted tetrazolyl group, an optionally halogenated lower alkyl group, an optionally halogenated lower alkenyl group, an optionally substituted arylalkyl group, an optionally substituted arylalkenyl group, an optionally substituted lower alkynyl group, an alkyl group substituted with an optionally protected carboxyl group or an alkenyl group substituted with an

optionally protected carboxyl group when X represents a group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  are each as defined above); or Y represents a group

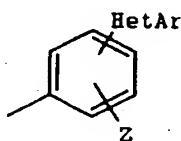
represented by formula:  [wherein  $R^5$

represents a hydroxyl group, an optionally halogenated lower alkoxy group, an arylalkoxy group or a group represented by formula:  $-NR^6R^7$  (wherein  $R^6$  and  $R^7$  may be the same or different from each other and each represents a hydrogen atom, an optionally halogenated lower alkyl group or an alkoxyalkyl group, or  $NR^6R^7$  may form a five- or six-membered heterocyclic ring having a carbon atom(s) and a nitrogen atom(s) optionally together with an oxygen atom(s) and/or a sulfur atom(s) as the ring-constituting atoms); and Z represents a hydrogen atom, an optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, an alkylthio group, an alkylsulfonyl group, an alkylsulfoxide group or a halogen atom)].

a group represented by formula:



(wherein  $R^8$  and  $R^9$  may be the same or different from each other and each represents a hydrogen atom, an alkylsulfonyl group, or an optionally halogenated lower alkyl group), a group represented by formula:

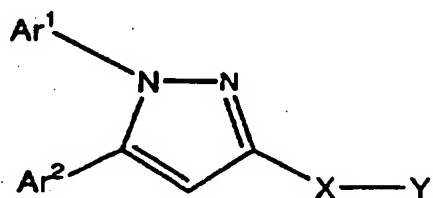


[wherein HetAr represents an optionally

substituted five- or six-membered heterocyclic ring having a carbon atom(s) together with at least one of a nitrogen atom(s), an oxygen atom(s) and a sulfur atom(s) as the ring-constituting atoms; and Z is as defined above] or an optionally substituted thienyl group when X represents a group represented by formula:  $>C=O$ .

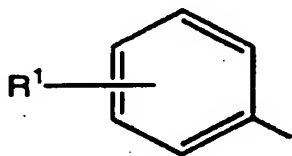
The present invention includes the following embodiments:

(1) a pyrazole derivative represented by the following formula (1) or a physiologically acceptable salt thereof:



(1)

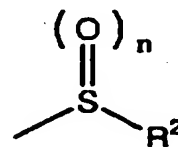
wherein  $\text{Ar}^1$  and  $\text{Ar}^2$  may be the same or different each other and each represents an optionally substituted heterocyclic group or a group represented by formula:



[wherein  $\text{R}^1$  represents a hydrogen

atom, an optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, a halogen

atom or a group represented by formula:



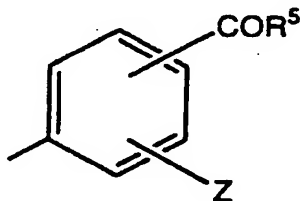
(wherein  $\text{R}^2$  represents a lower alkyl group or an optionally substituted amino group; and  $n$  represents an integer of 0, 1 or 2)];

$\text{X}$  represents a group represented by formula:  $>\text{CR}^3\text{R}^4$

(wherein  $\text{R}^3$  and  $\text{R}^4$  may be the same or different from each other and each represents a hydrogen atom, a hydroxyl group, an optionally halogenated lower alkoxy group, a halogen atom or an optionally protected carboxyl group; or  $\text{R}^3$  and  $\text{R}^4$  together with the carbon atom to which they are bonded may form a five- or six-membered ring); or a group represented by formula:  
 $>\text{C}=\text{O}$ ; and

Y represents an optionally substituted aryl group, an optionally substituted furyl group, an optionally substituted thienyl group, an optionally substituted pyridyl group, an optionally substituted thiazolyl group, a tetrazolyl group, an optionally halogenated lower alkyl group, an optionally halogenated lower alkenyl group, an optionally substituted arylalkyl group, an optionally substituted arylalkenyl group, an optionally substituted lower alkynyl group, an optionally protected carboxyalkyl group or an optionally protected carboxyalkenyl group when X represents a group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  may be the same or different from each other and each represents a hydrogen atom, a hydroxyl group, an optionally halogenated lower alkoxy group, a halogen atom or an optionally protected carboxyl group, or  $R^3$  and  $R^4$  together with the carbon atom to which they are bonded may form a five- or six-membered ring), while Y represents a group represented

by formula:

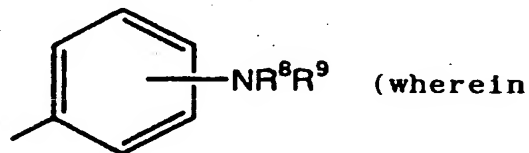


[wherein  $R^5$

represents a group represented by formula:  $-NR^6R^7$

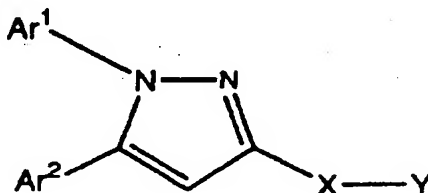
(wherein  $R^6$  and  $R^7$  may be the same or different from each other and each represents a hydrogen atom, a lower alkyl group or an alkoxyalkyl group, or  $R^6$  and  $R^7$  together with the nitrogen atom to which they are bonded may form a five- or six-membered ring), a hydroxyl group or a lower alkoxy group; and  $Z$  represents a hydrogen atom, a lower alkyl group, an optionally halogenated lower alkoxy group, an alkylthio group or a halogen atom] or a group

represented by formula:



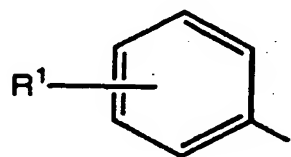
$R^8$  and  $R^9$  may be the same or different from each other and each represents a hydrogen atom, an alkylsulfonyl group or a lower alkyl group) when  $X$  represents a group represented by formula:  $>C=O$ ; and

(2) a pyrazole derivative represented by the following formula (ii) or a physiologically acceptable salt thereof:



(ii)

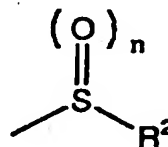
wherein Ar<sup>1</sup> and Ar<sup>2</sup> may be the same or different each other and each represents an optionally substituted heterocyclic group or a group represented by formula:



[wherein R<sup>1</sup> represents a hydrogen

atom, a lower alkyl group, an optionally halogenated lower alkoxy group, a halogen atom or a group

represented by formula:



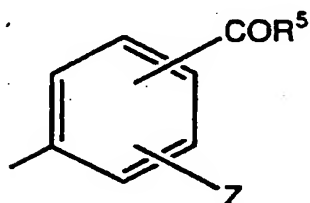
(wherein R<sup>2</sup>

represents a lower alkyl group and n represents an integer of 0, 1 or 2)]; and

Y represents an optionally substituted phenyl group, an optionally substituted furyl group, an optionally substituted thienyl group, an optionally substituted pyridyl group, an optionally substituted thiazolyl group, a tetrazole group, a lower alkyl group, a lower alkenyl group, an optionally substituted arylalkyl group, an optionally substituted arylalkenyl group, an optionally substituted alkynyl group, an optionally protected carboxyalkyl group or an optionally protected carboxyalkenyl group when X represents a

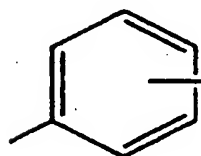


group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  may be the same or different from each other and each represents a hydrogen atom, a hydroxyl group, a lower alkoxy group, a halogen atom or an optionally substituted carboxyl group, or  $R^3$  and  $R^4$  may form a five- or six-membered ring by combining each other), while Y represents a group represented by formula:



[wherein  $R^5$  represents a group

represented by formula:  $-NR^6R^7$  (wherein  $R^6$  and  $R^7$  may be the same or different from each other and each represents a hydrogen atom, a lower alkyl group or an alkoxyalkyl group, or  $R^6$  and  $R^7$  may form a five- or six-membered ring by combining each other), a hydroxyl group or a lower alkoxy group; and Z represents a hydrogen atom, a lower alkyl group, an optionally halogenated lower alkoxy group, an alkylthio group or a halogen atom] or a group represented by formula:



(wherein  $R^8$  and  $R^9$  may be the same

or different from each other and each represents a

hydrogen atom, an alkylsulfonyl group or a lower alkyl group) when X represents a group represented by formula:  $>C=O$ .

Preferable examples of the pyrazole derivatives according to the present invention include those represented by the above formula (I) wherein  $Ar^1$  and  $Ar^2$  are each as defined above; X is a group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  are each as defined above) and Y is an optionally substituted phenyl group.

The present invention provides also a pharmaceutical composition comprising the above-described pyrazole derivative or the physiologically acceptable salt thereof, and a pharmacologically acceptable filler.

The present invention further provides a use of the above-described pyrazole derivative or the physiologically acceptable salt thereof for preparing a medicament being effective in treatment of a disease to which the simultaneous suppression of the production of both of a prostaglandin(s) and a leukotriene(s) is effective.

The present invention furthermore provides a method for preparing a medicament being effective in treatment of a disease to which the simultaneously

suppression of the production of both of a prostaglandin(s) and a leukotriene(s) is effective, which comprises using the above-described pyrazole derivative or the physiologically acceptable salt thereof as the active ingredient.

In addition, the present invention provides an antirheumatic comprising the above-described pyrazole derivative or the physiologically acceptable salt thereof as the active ingredient, and an anti-inflammatory/analgesic agent comprising the above-described pyrazole derivative or the physiologically acceptable salt thereof as the active ingredient.

Further scope and applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

#### Detailed Description of the Invention

In the optionally substituted heterocyclic group in the definition of Ar<sup>1</sup> and Ar<sup>2</sup> of the above formula

(I). the heterocyclic group means a five- or six-membered ring including 1 to 3 hetero atom(s) selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof include pyridyl group, pyrazinyl group, pyrimidinyl group, thienyl group, furyl group, pyrrolyl group and imidazolyl group. Among them, pyridyl group and thienyl group may be cited as preferable examples thereof.

The halogen atom in the definition of  $R^1$ ,  $R^3$ ,  $R^4$  and Z means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

In the optionally halogenated lower alkyl group in the definition of  $R^1$ ,  $R^2$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ , Y and Z, the lower alkyl group means a linear or branched alkyl group having 1 to 6 carbon atoms such as methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-amyl group, isopentyl group and neopentyl group. The expression "optionally halogenated" as used herein means that at least one of a fluorine atom, a chlorine atom, a bromine atom and an iodine atom may substitute for at least one hydrogen atom(s) in the above-mentioned lower alkyl groups. Examples of the halogenated lower alkyl groups include

trifluoromethyl group and dichloroethyl group. Among these optionally halogenated lower alkyl groups, particularly preferable examples include methyl group, ethyl group, propyl group and isopropyl group.

In the optionally halogenated lower alkoxy group in the definition of  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $Z$ , the lower alkoxy group means a linear or branched alkoxy group having 1 to 6 carbon atoms such as methoxy group, ethoxy group, n-propoxy group, isopropoxy group and n-butoxy group. The expression "optionally halogenated" as used herein means that at least one of a fluorine atom, a chlorine atom, a bromine atom and an iodine atom may substitute for at least one hydrogen atom(s) in the above-mentioned lower alkoxy groups. Examples of the halogenated lower alkoxy groups include trifluoromethoxy group, chloromethoxy group and dichloroethoxy group, among which those containing a fluorine atom such as trifluoromethoxy group are preferable. Particularly preferable examples of these optionally halogenated lower alkoxy groups include methoxy group and ethoxy group.

The alkoxyalkyl group in the definition of  $R^6$  and  $R^7$  means the one wherein the above-mentioned lower alkoxy group substitutes for a hydrogen atom in the above-mentioned lower alkyl group.

In the alkylthio group in the definition of Z, "alkyl" has the same meaning as that of the above-mentioned lower alkyl group.

In the alkylsulfonyl group in the definition of Z, R<sup>8</sup> and R<sup>9</sup>, "alkyl" has the same meaning as that of the above-mentioned lower alkyl group.

In the alkylsulfoxide group in the definition of Z, "alkyl" has the same meaning as that of the above-mentioned lower alkyl group.

In the optionally halogenated lower alkenyl group in the definition of Y, the lower alkenyl group means an alkenyl group having 2 to 6 carbon atoms and at least one double bond(s). The expression "optionally halogenated" as used herein means that at least one of a fluorine atom, a chlorine atom, a bromine atom and an iodine atom may substitute for at least one hydrogen atom(s) in the above-mentioned lower alkenyl group. Preferable examples of the optionally halogenated lower alkenyl group include vinyl group and allyl group.

In the optionally substituted lower alkynyl group in the definition of Y, the lower alkynyl group means an alkynyl group having 2 to 6 carbon atoms and at least one triple bond(s).

In the optionally substituted aryl group in the

definition of Y, the aryl group means, for example, phenyl group, 1-naphthyl group, 2-naphthyl group or anthracenyl group. Among these groups, a phenyl group may be cited as the most desirable one.

In the optionally substituted arylalkyl group in the definition of Y, the "aryl" has the same meaning as the aryl group defined above. In this case, the alkyl group has the same meaning as that of the lower alkyl group defined above.

In the optionally substituted arylalkenyl group in the definition of Y, the "aryl" has the same meaning as the aryl group defined above. In this case, the alkenyl group has the same meaning as that of the lower alkenyl group defined above.

In the arylalkoxy group in the definition of  $R^5$ , the "aryl" has the same meaning as the aryl group defined above. In this case, the alkyloxy group has the same meaning as that of the lower alkoxy group defined above.

In the optionally protected carboxyl group in the definition of  $R^3$  and  $R^4$ , the term "protected" means that the carboxyl group is turned into, e.g., an amide group or an ester group such as a lower alkyl ester and an aralkyl ester. That is to say, any group which can give a carboxyl group by a biochemical reaction in

vivo falls within this category. Examples of the protected carboxyl group include methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group and carboxamide group.

The expression "optionally substituted carboxyl group" has the same meaning as the "optionally protected carboxyl group" described above.

In the alkyl group substituted with an optionally protected carboxyl group in the definition of Y, the term "protected" has the same meaning as the one described above. In this case, the alkyl group has the same meaning as that of the above-mentioned lower alkyl group.

The expression "optionally protected carboxyalkyl group" has the same meaning as the "alkyl group substituted with an optionally protected carboxyl group" described above.

In the alkenyl group substituted with an optionally protected carboxyl group in the definition of Y, the term "protected" has the same meaning as the one described above. In this case, the alkenyl group has the same meaning as that of the above-mentioned lower alkenyl group.

The expression "optionally protected carboxy-alkenyl group" has the same meaning as the "alkenyl



group substituted with an optionally protected carboxyl group" described above.

In the five- or six-membered ring illustrated as  $CR^3R^4$ , the ring contains a carbon atom(s) and, optionally, an oxygen atom(s) as the ring-constituting atoms. Examples of the five- or six-membered ring herein include alicyclic hydrocarbons such as a cyclopentane ring and a cyclohexane ring, and heterocyclic rings containing at least one oxygen atom(s) such as a 1,3-dioxolane ring and a 1,3-dioxane ring.

In the five- or six-membered heterocyclic ring illustrated as  $NR^6R^7$ , the ring contains a carbon atom(s) and a nitrogen atom(s), and, optionally, an oxygen atom(s) and/or a sulfur atom(s) as the ring-constituting atoms. Examples of the five- or six-membered heterocyclic ring herein include heterocyclic rings containing one nitrogen atom such as a pyrrolidine ring and a piperidine ring, and heterocyclic rings containing at least two nitrogen atoms, at least one oxygen atom(s) and/or at least one sulfur atom(s) such as an imidazolidine ring, a pyrazoline ring, a pyrazine ring and a morpholine ring.

In the five- or six-membered heterocyclic ring

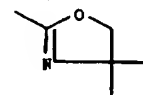
illustrated as HetAr, the ring contains a carbon atom(s) together with at least one of a nitrogen atom(s), an oxygen atom(s) and a sulfur atom(s) as the ring-constituting atoms. Examples of the five- or six-membered heterocyclic ring herein include a thiophene ring, a furan ring, a pyridine ring, a pyrimidine ring, an oxazole ring, a thiazole ring, a triazole ring, a tetrazole ring and a dihydrooxazole ring.

Of course, the above-mentioned five- or six-membered (heterocyclic) ring may have at least one substituent(s). Examples of the substituents include those which will be described below.

In the expression "optionally substituted heterocyclic group" in the definition of Ar<sup>1</sup> and Ar<sup>2</sup>, the expression "optionally substituted amino group" in the definition of R<sup>2</sup>, and the expressions "optionally substituted aryl group", "optionally substituted furyl group", "optionally substituted thienyl group", "optionally substituted pyridyl group", "optionally substituted thiazolyl group", "optionally substituted tetrazolyl group", "optionally substituted arylalkyl group", "optionally substituted arylalkenyl group", "optionally substituted lower alkynyl group", "optionally substituted thienyl group", "alkyl group

substituted with an optionally protected carboxyl group" and "alkenyl group substituted with an optionally protected carboxyl group" which are present in the definition of Y, the term "substituted" means that the above-mentioned heterocyclic group, alkyl group, alkenyl group or the like has at least one substituent(s). That is, a substituent substitutes for the hydrogen atom. Examples of the substituents include hydroxyl group; halogen atoms; optionally substituted lower alkyl groups such as halogenated lower alkyl groups, hydroxymethyl group, hydroxyaminomethyl group and hydroxyiminomethyl group; optionally substituted lower alkoxy groups such as n-propoxy group, tetrazolylmethoxy group and cyanomethoxy group; alkoxyalkyl groups such as 1,1-dimethoxymethyl group; optionally protected carboxyl groups; acyl groups such as formyl group, acetyl group, benzoyl group, lactoyl group, vanilloyl group and anisoyl group; cyano group; alkylsulfonyl groups; alkylsulfoxide groups; alkylsulfonamide groups; alkylthio groups; N-alkoxyimino groups; alkoxytetrahydropyranyl groups; tetrazoyl group; and

the group represented by the formula:



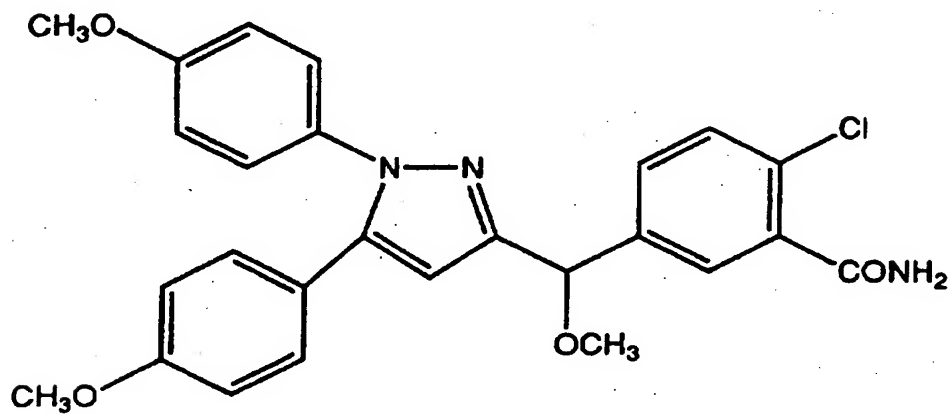
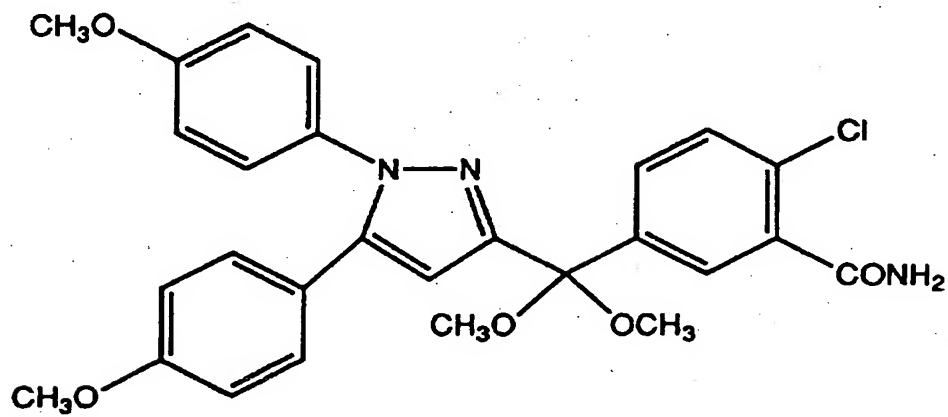
Each of the functional groups such as a heterocyclic group, an aryl group, an alkynyl group, an arylalkyl group, an arylalkenyl group and an amino group may have one or more substituents. Among optionally substituted thienyl groups herein, substituted thienyl groups are preferred.

In the present invention, the term "physiologically acceptable salt" means a nontoxic salt commonly employed in the art. Examples thereof include inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate, organic acid salts such as acetate, maleate, tartrate, methanesulfonate, benzenesulfonate and toluenesulfonate and salts of amino acids such as arginine, aspartic acid and glutamic acid. Also metal salts such as sodium salt, potassium salt, calcium salt and magnesium salt fall within the category of the physiologically acceptable salts in the present invention.

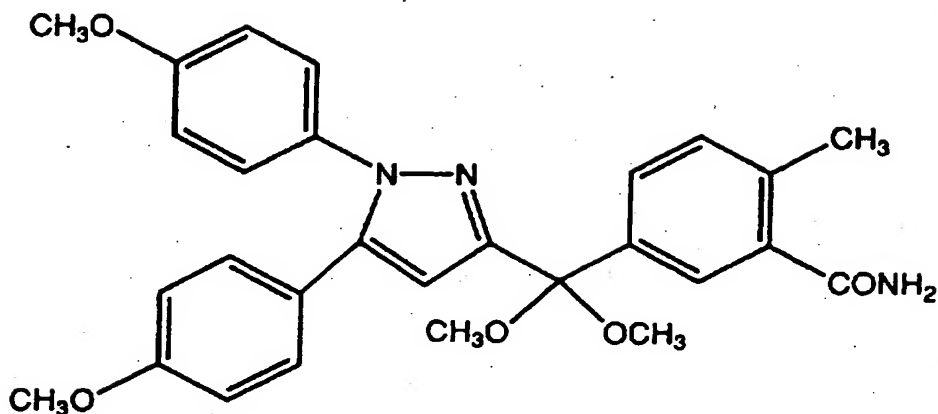
Still more preferable examples of the compounds according to the present invention include pyrazole derivatives represented by the above-mentioned formula (I) wherein X is a group represented by  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  are each as defined above), Y is an optionally substituted phenyl group, and  $Ar^1$  and  $Ar^2$  are each as defined above; and physiologically

acceptable salts thereof.

The most desirable examples of the compounds according to the present invention are the following ones and physiologically acceptable salts thereof:



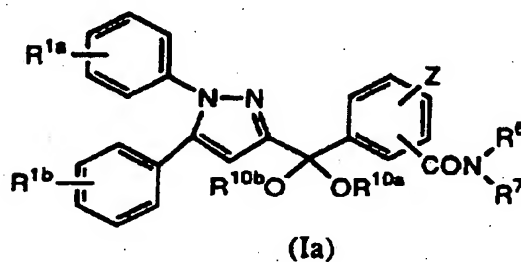
and



The compounds of the present invention can be easily prepared by a known reaction or a combination of known reactions. Now, typical examples of the processes for the production of the compounds of the present invention will be described.

#### Production process 1

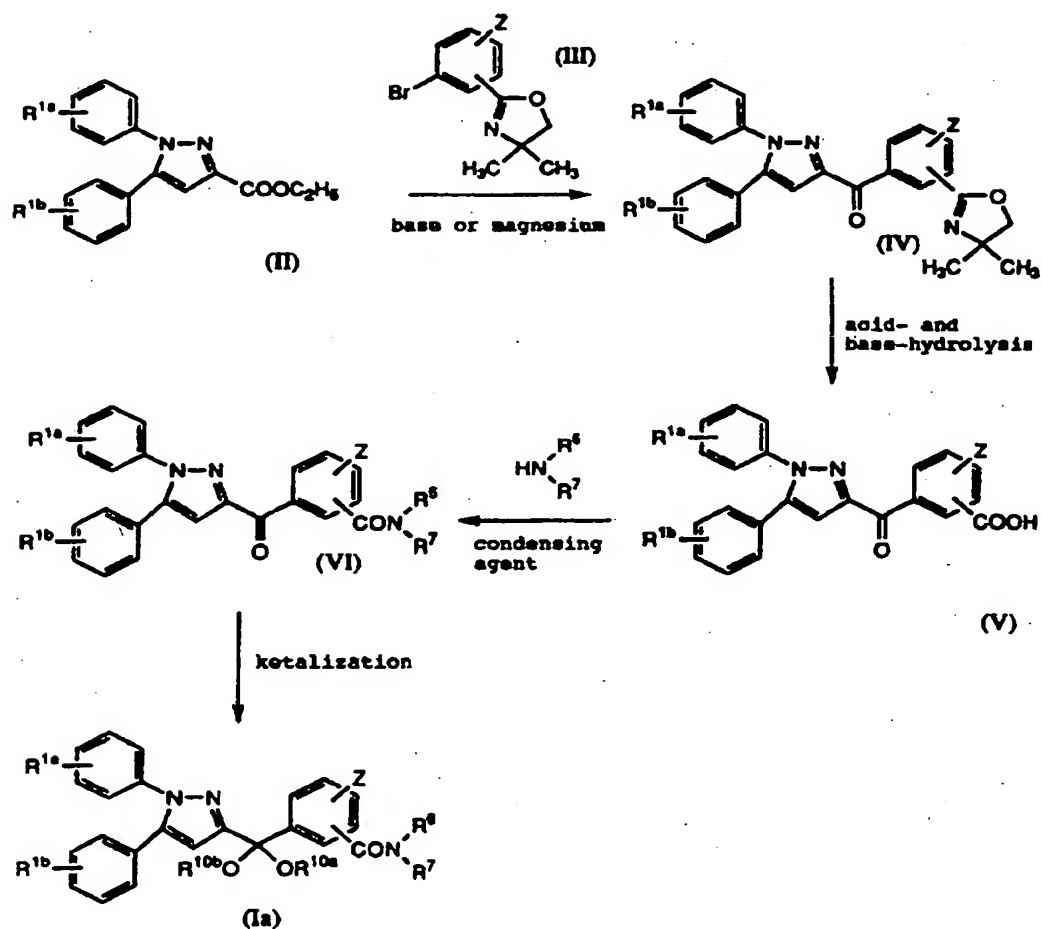
Among the compounds represented by formula (I), those represented by formula (Ia):



wherein  $R^{1a}$  and  $R^{1b}$  have each the same meaning as the one of  $R^1$  as defined above;

$Z$ ,  $R^6$  and  $R^7$  are each as defined above; and

$R^{10a}$  and  $R^{10b}$  represent each a lower alkyl group, or  $R^{10a}$  and  $R^{10b}$  may form a ring together with the oxygen atoms to which they are bonded and the carbon atom to which the oxygen atoms are bonded; can be prepared by the following process:



wherein  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$ ,  $R^{10a}$ ,  $R^{10b}$  and Z are each as defined above.

Namely, the first step comprises reacting a pyrazole derivative represented by formula (II) with a compound represented by formula (III) in a solvent in the presence of a base or metallic magnesium to thereby give a compound represented by formula (IV). The compound represented by formula (II) and the one represented by formula (III) can be prepared each by a conventional method. For example, the compound represented by formula (II) can be prepared by methods described in, for example, J. Heterocyclic Chem., 26, 1389 (1989) and Japanese Patent Publication-A No. 64-52758, while the compound represented by formula (III) can be prepared by methods described in, for example, J. Am. Chem. Soc., 92, 6646 (1970).

Examples of the solvent to be used in this step include dry solvents such as diethyl ether and tetrahydrofuran, while examples of the base to be used therein include n-butyllithium, sec-butyllithium and lithium diisopropylamide. This reaction is preferably effected in an inert gas (for example, nitrogen gas) atmosphere within a temperature range of from -78 to 25°C.

In the next step, the compound represented by formula (IV) is hydrolyzed successively with an acid and a base in an appropriate solvent such as methanol



and ethanol in accordance with a method described in, for example, J. Am. Chem. Soc., 92, 6646 (1970) to thereby give a compound represented by formula (V). In this step, it is preferable to use, for example, aqueous hydrochloric acid or aqueous sulfuric acid as the acid, and an aqueous solution of, for example, sodium hydroxide or potassium hydroxide as the base.

The reaction temperature falls within a range of from room temperature to the boiling point of the solvent.

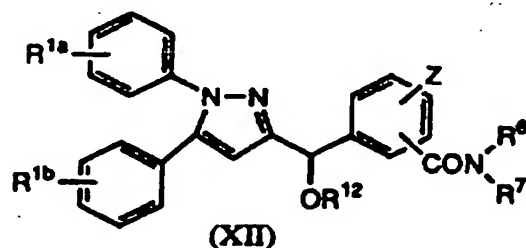
In the next step, the compound represented by formula (V) is reacted in the presence of an appropriate condensing agent [for example, a chloroformic acid ester or a water-soluble carbodiimide such as 1-ethyl-3-(dimethylamino-propyl)carbodiimide] with ammonia or an amine such as morpholine to thereby give a compound represented by formula (VI). This reaction can be effected in an appropriate solvent such as N,N-dimethylformamide and tetrahydrofuran with the use of an appropriate condensing aid such as 1-hydroxybenzotriazole and N-hydroxysuccinimide. The reaction temperature falls within a range of from 0°C to room temperature.

Subsequently, the compound (VI) is reacted in the presence of an acid catalyst (for example, p-toluene-

sulfonic acid or sulfuric acid) with an alcohol such as methanol and ethanol, a diol such as ethylene glycol and propylene glycol or a trialkyl orthoformate to thereby give the target compound represented by formula (Ia). In this reaction, use is made of, for example, methanol, ethanol or toluene as the solvent. The reaction temperature falls within a range of from room temperature to the boiling point of the solvent.

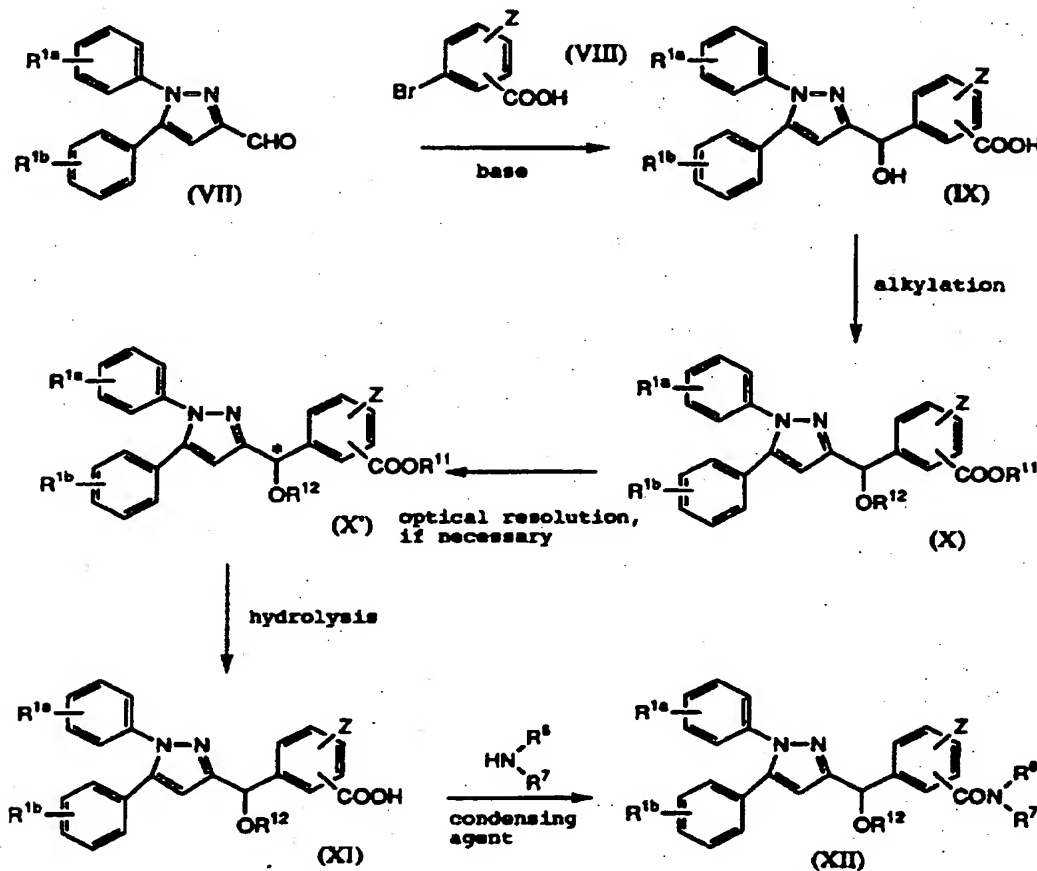
#### Production process 2

Compounds represented by formula (XII):



wherein  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$  and  $Z$  are each as defined above, and  $R^{12}$  represents an optionally halogenated lower alkyl group:

can be prepared by the following method:



wherein  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$ ,  $R^{12}$  and  $Z$  are each as defined above, and  $R^{11}$  represents an optionally halogenated lower alkyl group or an aralkyl group.

In the first step, a bromobenzoic acid derivative represented by formula (VIII) is treated in an appropriate solvent with 2 equivalents of a base such as n-butyllithium, sec-butyllithium and lithium isopropylamide and then reacted with a compound

represented by formula (VII) to thereby give a compound represented by formula (IX).

This reaction is effected in an inert gas (for example, nitrogen gas) atmosphere with the use of a dry solvent such as diethyl ether and tetrahydrofuran at a temperature of from -100 to 25°C.

In the next step, the compound represented by formula (IX) obtained in the above step is reacted in a solvent such as N,N-dimethylformamide and tetrahydrofuran in the presence of an appropriate base with at least 2 equivalents of an alkyl halide to thereby give a compound represented by formula (X). In this step, use can be made of, for example, sodium hydride, t-butoxypotassium or sodium hydroxide as the base. The reaction temperature preferably falls within a range of from the ice temperature to the boiling point of the solvent.

When the target compound (XII) is a racemic modification, then the compound (X) thus obtained is subjected to the next treatment as such. When the compound (XII) is an optically active substance, then the compound (X) is optically resolved into enantiomers by a conventional method by using, for example, a chiral HPLC. Next, the compound (X) or (X') is hydrolyzed by reacting it with a base such as

sodium hydroxide and potassium hydroxide in a water-containing solvent such as water/methanol to thereby give a compound represented by formula (XI). In the hydrolysis, the reaction temperature usually falls within a range of from room temperature to the boiling point of the solvent.

Then the compound (XI) obtained in the above step is reacted in the presence of an appropriate condensing agent [for example, a chloroformic acid ester or a water-soluble carbodiimide such as 1-ethyl-3-(dimethylaminopropyl)carbodiimide] with ammonia or an amine such as morpholine to thereby give the target compound represented by formula (XII). In this reaction, use can be made of an appropriate condensing aid such as N,N-dimethylformamide and tetrahydrofuran, and the reaction temperature usually falls within a range of from 0°C to room temperature.

#### Production process 3

Compounds represented by formula (I), wherein X represents a group represented by formula:  $>CR^3R^4$  (wherein at least one of  $R^3$  and  $R^4$  is a lower alkoxy group); Y represents a group other than those having a carbonyl-containing group such as a group represented by formula:  $-COR^5$ ; and others are each as defined above, can be prepared by the following process in

accordance with the production process 2.

(Step 1)

In accordance with the first step of the production process 2, the compound (VII) is reacted with an alkyl halide, an aryl halide or a heteroaryl halide in the presence of magnesium or a base such as an alkyllithium to thereby give a compound according to the compound (IX).

(Step 2)

In accordance with the next step of the production process 2, the compound obtained in the above step 1 is subjected to an alkylation to thereby substitute alkoxy groups for hydroxyl groups, thus giving a compound according to the compound (X). The compound thus obtained may be optically resolved into the enantiomers, if necessary.

(Step 3)

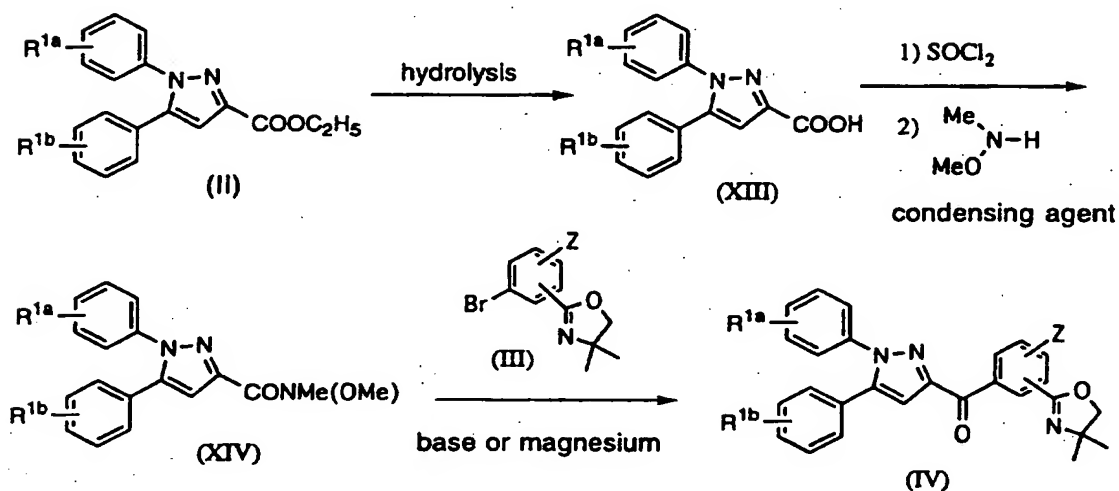
The compound obtained in the above step 1 is oxidized to thereby give a ketone.

(Step 4)

The ketone obtained in the above step 3 is treated in the presence of a suitable alcohol such as an orthoformate, methanol, ethanol, ethylene glycol and propylene glycol, and an acid catalyst to thereby give a ketal.

Production process 4

Compounds represented by formula (IV) wherein  $R^{1a}$  and  $R^{1b}$  are each as defined above can also be prepared by the following process:



wherein  $R^{1a}$ ,  $R^{1b}$  and Z are each as defined above.

Namely, the first step comprises hydrolyzing a pyrazole derivative represented by formula (II) with a base in a suitable solvent such as methanol and ethanol to thereby give a compound represented by formula (XIII). Examples of the base to be used herein include sodium hydroxide and potassium hydroxide, and the base is preferably used in the form of an aqueous solution thereof. The reaction is effected at a temperature in a range of from room temperature to the boiling point of the solvent used.

In the next step, the compound represented by formula (XIII) is converted into an acid halide with a suitable reagent such as thionyl chloride in accordance with a method described in, for example, J. Org. Chem., 56, 3750 (1991), and then the acid halide is reacted with methoxymethylamine in the presence of a condensing agent to thereby give a compound represented by formula (XIV).

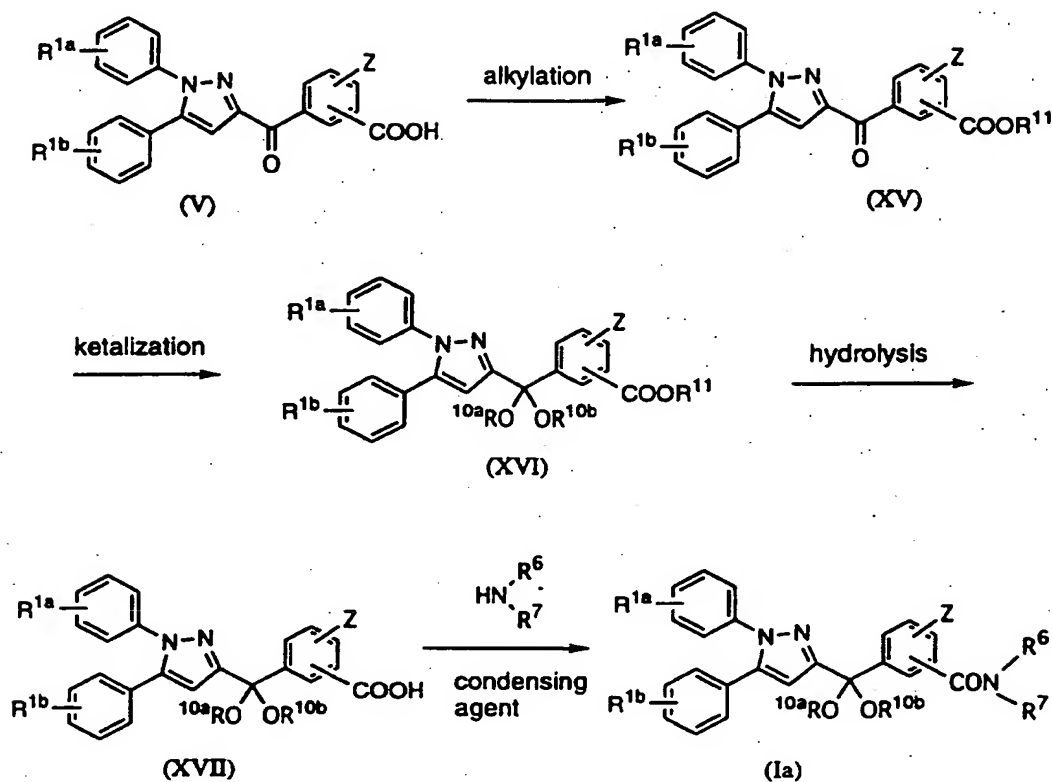
Subsequently, the pyrazole derivative represented by formula (XIV) is reacted in a suitable solvent in the presence of a base or metallic magnesium with a compound represented by formula (III) to thereby give a compound represented by formula (IV).

Examples of the solvent to be used in this step include dry solvents such as diethyl ether and tetrahydrofuran, while examples of the base to be used therein include n-butyllithium, sec-butyllithium and lithium diisopropylamide. This reaction is preferably effected in an inert gas (for example, nitrogen gas) atmosphere within a temperature range of from -78 to 25°C.

#### Production process 5

Compounds represented by formula (Ia) wherein  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$ ,  $R^{10a}$ ,  $R^{10b}$  and Z are each as defined above can also be prepared by the following process:





wherein  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$ ,  $R^{10a}$ ,  $R^{10b}$ ,  $R^{11}$  and  $Z$  are each as defined above.

In the first step, the compound represented by formula (V) obtained in the course of production process 1 is reacted in a solvent such as N,N-dimethylformamide and tetrahydrofuran in the presence of an appropriate base with an alkyl halide to thereby give a compound represented by formula (XV). In this step, it is preferable to use, for example, sodium hydride, t-butoxypotassium or sodium

hydroxide as the base. The reaction temperature preferably falls within a range of from the ice temperature to the boiling point of the solvent.

In the second step, the compound represented by formula (XV) obtained in the above first step is reacted in an appropriate solvent such as methanol, ethanol and toluene in the presence of an acid catalyst such as p-toluenesulfonic acid and sulfuric acid with an alcohol or a trialkyl orthoformate to thereby give a compound represented by formula (XVI).

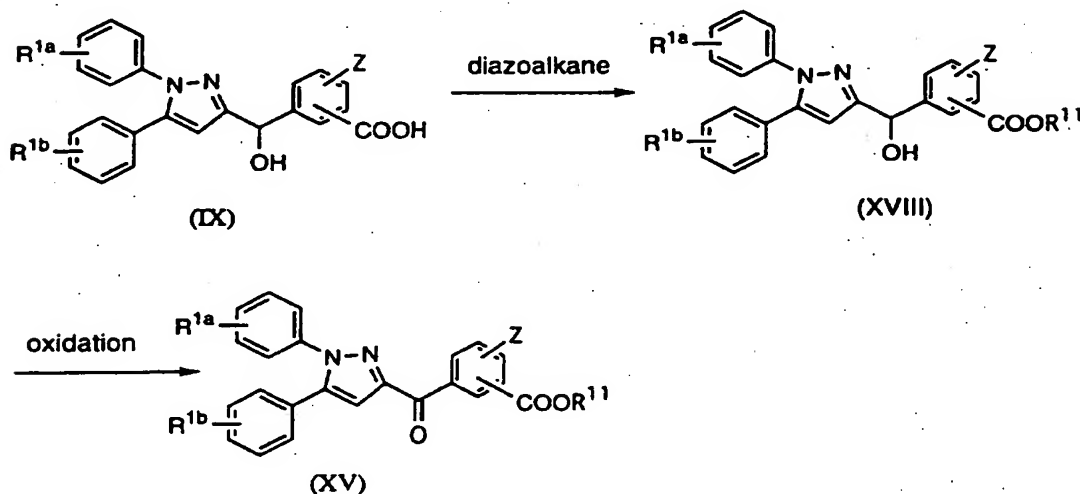
In the third step, the compound represented by formula (XVI) obtained in the above second step is hydrolyzed with a base in a suitable solvent such as methanol and ethanol to thereby give a compound represented by formula (XVII). Examples of the base to be used herein include sodium hydroxide and potassium hydroxide, and the base is preferably used in the form of an aqueous solution thereof. The reaction is effected at a temperature in a range of from room temperature to the boiling point of the solvent used.

Further, in the last step, the compound represented by formula (XVII) is reacted in the presence of an appropriate condensing agent [for example, a chloroformic acid ester or a water-soluble

carbodiimide such as 1-ethyl-3-(dimethylaminopropyl)-carbodiimide] with ammonia or an amine such as morpholine to thereby give a compound represented by formula (Ia). This reaction can be effected in an appropriate solvent such as N,N-dimethylformamide and tetrahydrofuran with the use of an appropriate condensing aid such as 1-hydroxybenzotriazole and N-hydroxysuccinimide. The reaction temperature falls within a range of from 0°C to room temperature.

#### Production process 6

Compounds represented by formula (XV) wherein R<sup>1a</sup>, R<sup>1b</sup>, R<sup>11</sup> and Z are each as defined above can also be prepared by the following process:



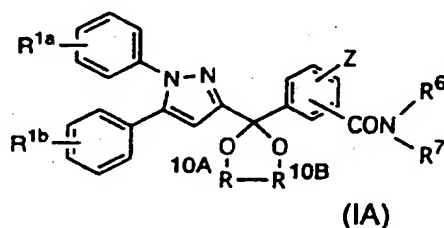
wherein R<sup>1a</sup>, R<sup>1b</sup>, R<sup>11</sup> and Z are each as defined above.

In the first step, the compound represented by formula (IX) is reacted in a suitable solvent with a suitable diazoalkane such as diazomethane, diphenyldiazomethane and trimethylsilyldiazomethane to thereby give a compound represented by formula (XVIII). The reaction temperature falls within a range of from 0°C to the boiling point of the solvent used.

In the next step, the compound represented by formula (XVIII) is oxidized with an appropriate oxidizing agent such as manganese dioxide and dimethylsulfoxide/oxalylchloride/triethylamine to thereby give a compound represented by formula (XV).

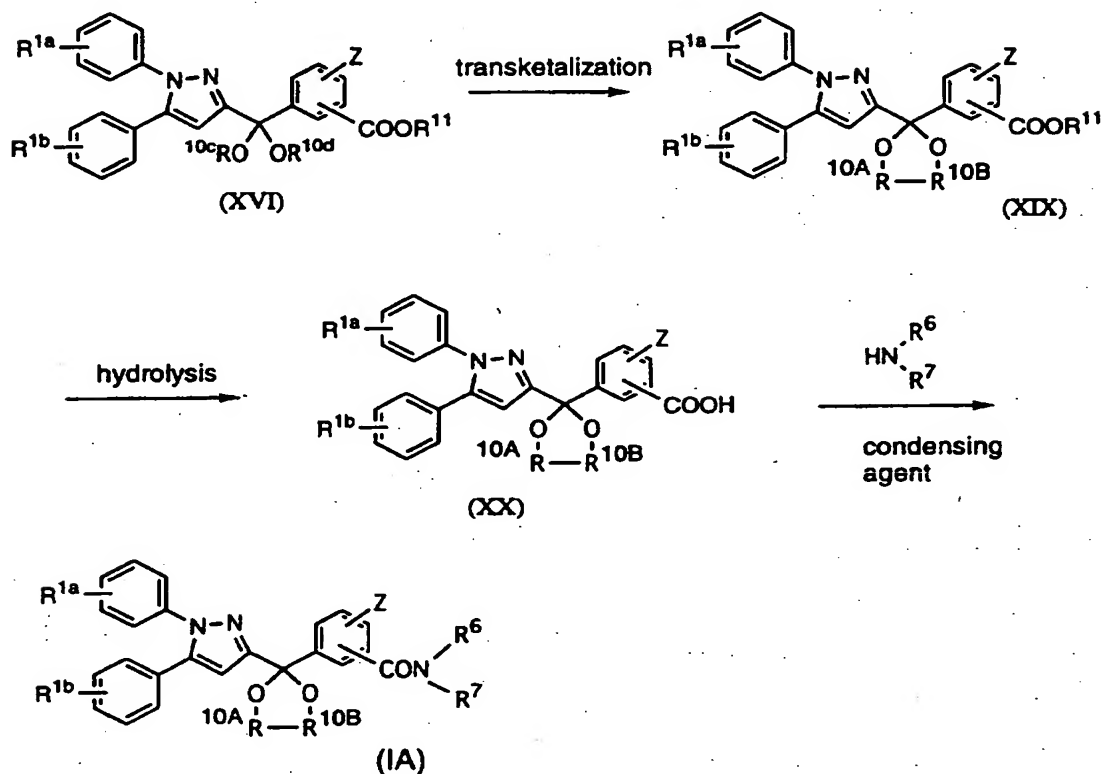
#### Production process 7

Compounds represented by formula (IA):



(wherein  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$  and  $Z$  are each as defined above; and  $-R^{10A}-R^{10B}-$  represents an alkylene group), i.e., compounds represented by formula (Ia) which can be produced by production process 1 with the proviso that  $R^{10a}$  and  $R^{10b}$  form a ring together with the oxygen atoms to which they are bonded and the carbon atom to

which the oxygen atoms are bonded, can also be prepared by the following process:



wherein  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$ ,  $-R^{10A}-R^{10B}-$ ,  $R^{11}$  and  $Z$  are each as defined above; and  $R^{10c}$  and  $R^{10d}$  represent each a lower alkyl group.

(Step 1)

In this step, the compound represented by formula (XVI) obtained in the course of production process 5 is reacted in an appropriate solvent such as benzene and toluene in the presence of an acid catalyst such

as p-toluenesulfonic acid and sulfuric acid with an appropriate diol such as ethylene glycol and propylene glycol to thereby give a compound having, e.g., a 1,3-dioxolan ring or a 1,3-dioxane ring represented by formula (XIX). The reaction temperature falls within a range of from room temperature to the boiling point of the solvent used.

(Step 2)

In this step, the compound represented by formula (XIX) obtained in the above step 1 is hydrolyzed with a base in a suitable solvent such as methanol and ethanol to thereby give a compound represented by formula (XX). Examples of the base to be used herein include sodium hydroxide and potassium hydroxide, and the base is preferably used in the form of an aqueous solution thereof. The reaction is effected at a temperature in a range of from room temperature to the boiling point of the solvent used.

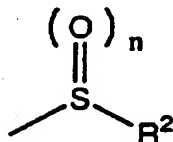
(Step 3)

Further, in this step, the compound represented by formula (XX) obtained in the above step 2 is reacted in the presence of an appropriate condensing agent [for example, a chloroformic acid ester or a water-soluble carbodiimide such as 1-ethyl-3-(dimethylaminopropyl)carbodiimide] with ammonia or an

amine such as morpholine to thereby give a compound represented by formula (IA). This reaction can be effected in an appropriate solvent such as N,N-dimethylformamide and tetrahydrofuran with the use of an appropriate condensing aid such as 1-hydroxy-benzotriazole and N-hydroxysuccinimide. The reaction temperature falls within a range of from 0°C to room temperature.

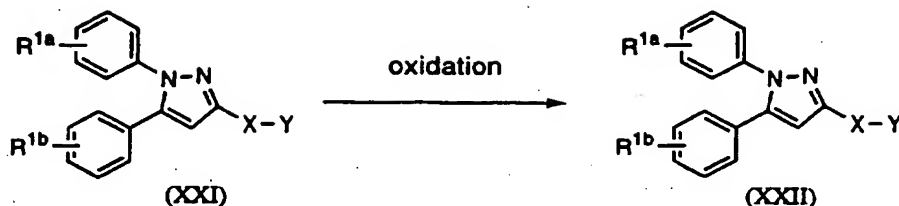
#### Production process 8

Among compounds represented by formula (I) which can be produced by the above production processes 1 to 7, those represented by formula (I), wherein R<sup>1a</sup> or R<sup>1b</sup> represents a group represented by formula:



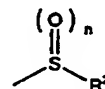
(wherein R<sup>2</sup> represents an optionally

halogenated lower alkyl group or an optionally substituted amino group; and n represents an integer of 0, 1 or 2); and X and Y are each as defined above, can be prepared by oxidizing the compounds represented by formula (I), wherein R<sup>1a</sup> or R<sup>1b</sup> represents a group represented by formula: -SR<sup>2</sup> (wherein R<sup>2</sup> is as defined above); and X and Y are each as defined above, as described in the following process:



wherein  $R^{1a}$  or  $R^{1b}$  represents a group represented by formula:  $-SR^2$

wherein  $R^{1a}$  or  $R^{1b}$  represents a group represented by formula:



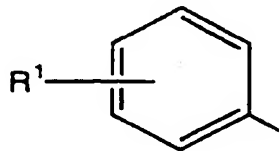
wherein  $R^2$ , X and Y are each as defined above.

In this step, the alkylthio group of a compound represented by formula (XXI) is oxidized with, for example, OXONE ( $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ ) to thereby convert it into an alkylsulfoxide or alkylsulfonyl group.

#### Production process 9

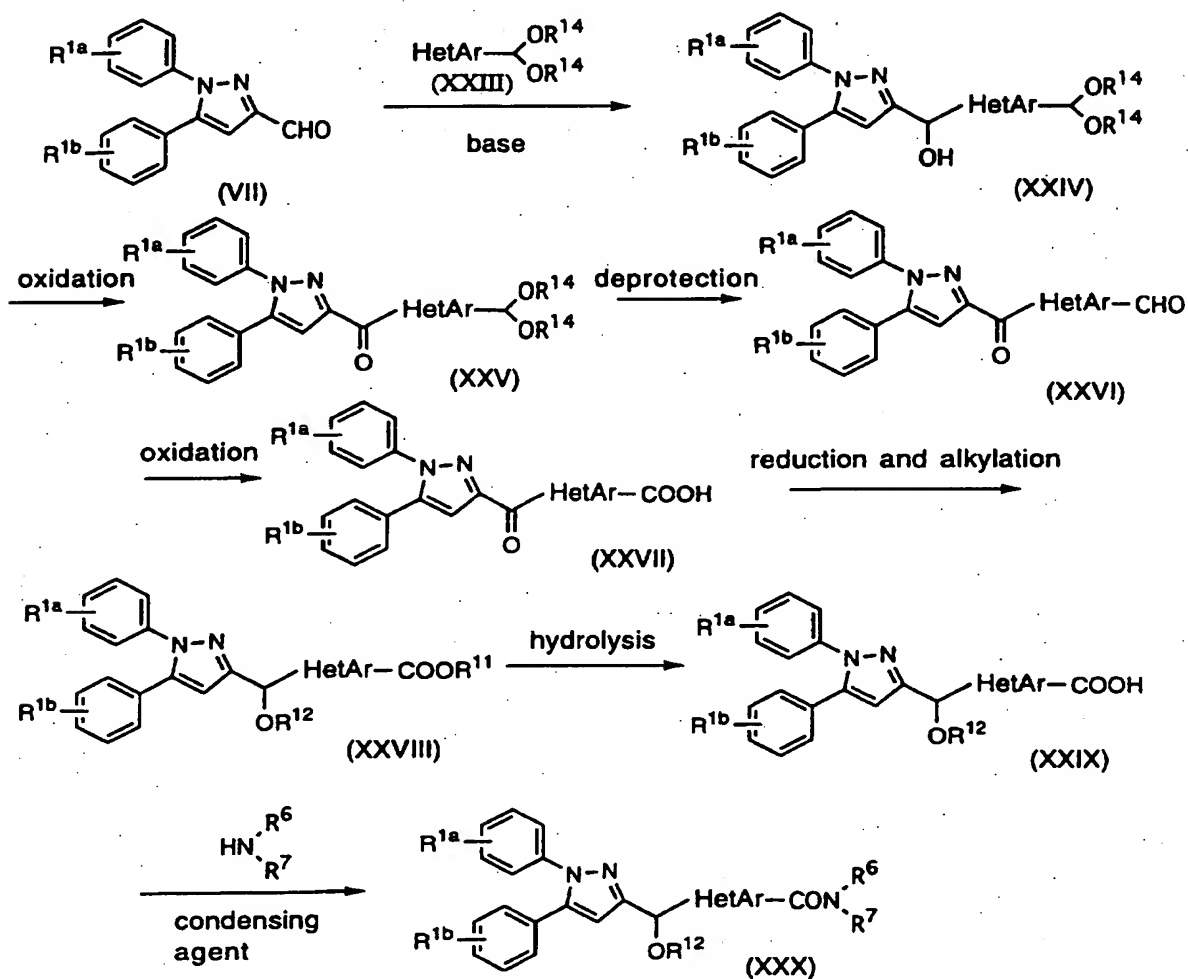
Compounds represented by formula (I), wherein X represents a group represented by formula:  $>C(H)OR^{12}$  (wherein  $R^{12}$  is as defined above); Y represents a furyl, thienyl, pyridyl or thiazolyl group which has an optionally protected carboxyl group such as a carboxyl group, an alkoxycarbonyl group and a carboxamide group; and  $Ar^1$  and  $Ar^2$  represent each a

group represented by formula:





(wherein  $R^1$  is as defined above), can be prepared by the following process in accordance with the production processes 1 and 2:



wherein HetAr represents an optionally substituted furyl group, an optionally substituted thienyl group, an optionally substituted pyridyl group or an optionally

substituted thiazolyl group;  $R^{14}$  represents a lower alkyl group; and  $R^{1a}$ ,  $R^{1b}$ ,  $R^6$ ,  $R^7$ ,  $R^{11}$  and  $R^{12}$  are each as defined above.

In the first step, a compound represented by formula (VII) is reacted in a solvent in the presence of a base or metallic magnesium with a compound represented by formula (XXIII) to thereby give a compound represented by formula (XXIV). Examples of the solvent to be used in this step include dry solvents such as diethyl ether and tetrahydrofuran, while examples of the base to be used therein include n-butyllithium, sec-butyllithium and lithium diisopropylamide. This reaction is preferably effected in an inert gas (for example, nitrogen gas) atmosphere within a temperature range of from -78 to 25°C.

In the next step, the compound represented by formula (XXIV) is oxidized with an appropriate oxidizing agent such as manganese dioxide and dimethylsulfoxide/oxalylchloride/triethylamine to thereby give a compound represented by formula (XXV).

Subsequently, the compound represented by formula (XXV) is reacted with water in the presence of an acid catalyst such as p-toluenesulfonic acid and sulfuric acid to thereby give a compound represented by formula

(XXVI). Examples of the solvent to be used in this step include methanol, ethanol and toluene. The reaction is effected at a temperature in a range of from room temperature to the boiling point of the solvent used.

Next, the compound represented by formula (XXVI) is oxidized with an appropriate oxidizing agent such as sodium chlorite to thereby give a compound represented by formula (XXVII).

The compound represented by formula (XXVII) is reduced with an appropriate reducing agent such as sodium borohydride, and then the compound thus obtained is subjected to alkylation with an appropriate alkylating agent such as an alkyl halide to thereby give a compound represented by formula (XXVIII). Examples of the solvent to be used in this step include methanol, ethanol and toluene. The reaction is effected at a temperature in a range of from room temperature to the boiling point of the solvent used.

Thereafter, the compound represented by formula (XXVIII) is hydrolyzed with a base in a water-containing solvent to thereby give a compound represented by formula (XXIX).

In the last step, the compound represented by

formula (XXIX) is reacted in the presence of an appropriate condensing agent such as a chloroformic acid ester and a water-soluble carbodiimide with ammonia or an amine such as morpholine to thereby give a compound represented by formula (XXX).

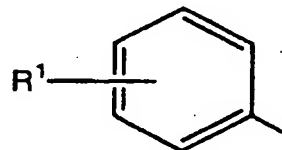
Production process 10

Compounds represented by formula (I), wherein X represents a group represented by formula:

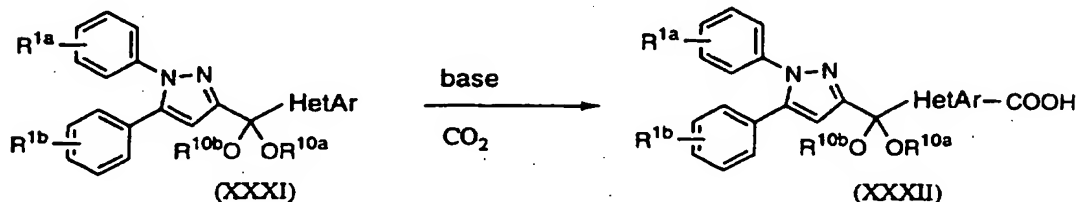


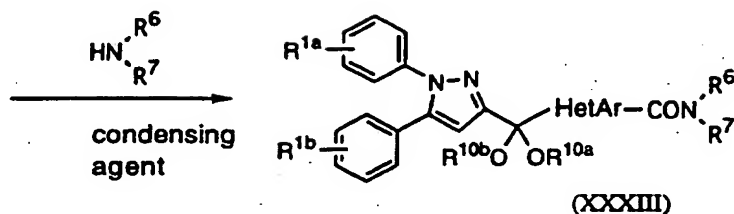
(wherein  $R^{10a}$  and  $R^{10b}$  are each as defined above); Y represents a furyl, thienyl, pyridyl or thiazolyl group which has an optionally protected carboxyl group such as carboxyl group, an alkoxycarbonyl group and a carboxamide group; and  $Ar^1$  and  $Ar^2$  represent each a

group represented by formula:



(wherein  $R^1$  is as defined above), can be prepared by the following process in accordance with the production processes 1 and 2:





wherein HetAr represents an optionally substituted furyl group, an optionally substituted thienyl group, an optionally substituted pyridyl group or an optionally substituted thiazolyl group; and  $\text{R}^{1\text{a}}$ ,  $\text{R}^{1\text{b}}$ ,  $\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^{10\text{a}}$  and  $\text{R}^{10\text{b}}$  are each as defined above.

In the first step, a compound represented by formula (XXXI) is reacted with carbon dioxide in the presence of a base to thereby give a compound represented by formula (XXXII). Examples of the solvent to be used in this step include dry solvents such as diethyl ether and tetrahydrofuran, while examples of the base to be used therein include n-butyllithium, sec-butyllithium and lithium diisopropylamide. This reaction is preferably effected in an inert gas (for example, nitrogen gas) atmosphere within a temperature range of from  $-78$  to  $25^\circ\text{C}$ .

In the next step, the compound represented by formula (XXXII) is reacted in the presence of an

appropriate condensing agent such as a chloroformic acid ester and a water-soluble carbodiimide with ammonia or an amine such as morpholine to thereby give a compound represented by formula (XXXIII).

To explain the usefulness of the compounds according to the present invention, the following pharmacological experimental example will be given.

Pharmacological Experimental Example

Effect of suppressing the production of leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in rat peritoneal infiltrated cells

Experimental method:

10 ml of a 6% (w/v) solution of glycogen (Type II from Oyster, Sigma) in physiological saline was intraperitoneally injected into a male Fisher rat weighing 150 to 200 g. After 20 to 24 hours, the peritoneal infiltrated cells were recovered from this rat, washed and suspended in Hank's balanced salt solution (HBSS) at a concentration of  $5 \times 10^6$ /ml. Then this cell suspension was pipetted into a 96-well culture plate (Falcon<sup>TM</sup>), into which a test drug diluted to a definite concentration had been pipetted at a ratio of 15  $\mu$ l/well, at a ratio of 120  $\mu$ l/well. After incubating this plate at 37°C for 10 minutes, A-23817 (calcium ionophore, CALIBIOCHEM<sup>TM</sup>) was added to

each of wells to give a final concentration of 4  $\mu\text{M}$ . After reacting for additional 10 minutes at 37°C, the plate was placed on ice and a BW-755C solution was added to each of wells to give a final concentration of 100  $\mu\text{M}$ . This plate was centrifuged at 2,800 rpm for 10 minutes and the supernatants were each collected. Then  $\text{LTB}_4$  and  $\text{PGE}_2$  in the supernatants were each assayed by the enzyme immunoassay method with the use of an EIA kit manufactured by AMERSHAM.

Result:

Table 1 shows the effects (expressed in  $\text{IC}_{50}$ ) of each compound (shown in the example number) on suppressing the production of  $\text{LTB}_4$  and  $\text{PGE}_2$ .

Table 1 Effect on the production of  $\text{LTB}_4$  and  $\text{PGE}_2$  in rat peritoneal infiltrated cells

Ex. No.	$\text{IC}_{50}$ ( $\mu\text{M}$ )	
	$\text{PGE}_2$	$\text{LTB}_4$
Ex. 8	0.0017	0.22
Ex. 21	0.014	0.0033
Ex. 24	0.034	0.004
Ex. 25	0.0088	0.02
Ex. 60 [(+) cpd.]	0.0046	>0.1
Ex. 60 [(-) cpd.]	0.0067	0.0056
Ex. 77	0.031	0.002

The above-mentioned pharmacological experimental example has clarified that the compounds of the present invention suppress the production of  $LTB_4$  and  $PGE_2$  simultaneously. Accordingly, the compounds of the present invention are efficacious in relieving inflammation and pain in rheumatoid arthritis, arthrosis deformans, shoulder periarthrititis, neck-shoulder-arm disorder syndrome, lumbago, etc. and useful as an anti-inflammatory/analgesic agent for postoperative or posttraumatic period.

When the compound of the present invention is to be administered for preventing and/or treating these diseases, it may be orally administered in the form of, for example, tablets, powders, granules, capsules or syrups. Alternatively, it may be parenterally administered in the form of, for example, suppositories, injections or external preparations. Such preparations for oral or parenteral administration may be produced by a conventional method with the use of pharmaceutically acceptable carriers commonly employed in the art.

The preparation of the compound of the present invention thus obtained may be orally administered to a patient usually in a dose of from about 0.1 to 1,000 mg, preferably from about 10 to 1,000 mg, per day in 1



to 5 portions, preferably 2 or 3 portions. In the case of parenteral administration, in particular, in the form of an injection, it is usually administered in a dose of from about 1 to 3,000  $\mu\text{g/kg}$ , preferably from about 3 to 1,000  $\mu\text{g/kg}$ , per day as a standard. The dose may be appropriately determined by considering various factors including the age and sex of the patient, type of conditions, severity, administration route, sensitivity to medicines and the occurrence and type of complication.

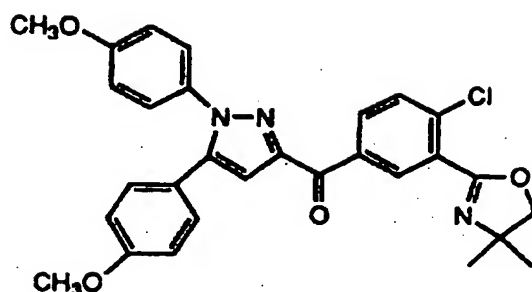
As described above, the compounds of the present invention have the effect of simultaneously suppressing the production of  $\text{LTB}_4$  and  $\text{PGE}_2$ . Moreover, these compounds of the present invention are characterized by the low toxicity and high safety.

#### Examples

The present invention will now be described in more detail with reference to the following examples which should not be considered to limit the scope of the present invention.

##### Example 1

1,5-Bis(4-methoxyphenyl)pyrazol-3-yl 3-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)]-4-chlorophenyl ketone



10.8 g (30.5 mmol) of ethyl 1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxylate and 13.2 g (45.8 mmol) of 2-(5-bromo-2-chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole were dissolved in 250 ml of dry tetrahydrofuran and the obtained mixture was stirred under a nitrogen gas stream at  $-78^{\circ}\text{C}$ . To the reaction mixture was slowly added 28.6 ml (45.8 mmol) of a 1.6 M solution of n-butyllithium in hexane for 30 minutes. Then the temperature of the reaction mixture was slowly elevated to  $0^{\circ}\text{C}$  for 3.5 hours. Then 250 ml of water was added to the reaction mixture, followed by the extraction with ethyl acetate. The organic phase was washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After filtering, the filtrate was distilled to remove the solvent and the residue was crystallized by adding a small amount of diisopropyl ether. The crystals were collected by filtration and washed with diisopropyl ether thrice to thereby give 8.7 g of crude

1,5-bis(4-methoxyphenyl)pyrazol-3-yl 3-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)]-4-chlorophenyl ketone as pale yellow crystals. Some of these crystals were recrystallized from ethanol to thereby give pure 1,5-bis(4-methoxyphenyl)pyrazol-3-yl 3-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)]-4-chlorophenyl ketone in the form of white crystals.

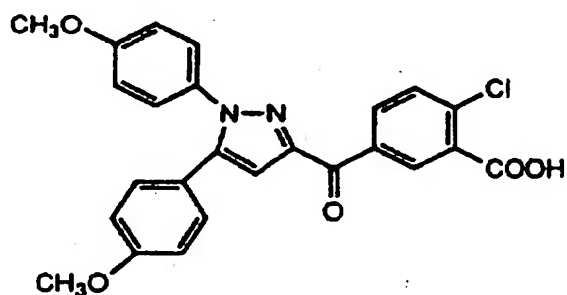
NMR(CDCl<sub>3</sub>) $\delta$ :

1.45(s, 6H), 3.82(s, 3H), 3.83(s, 3H), 4.17(s, 2H), 6.86(m, 2H, AA'BB'), 6.88(m, 2H, AA'BB'), 7.11(s, 1H), 7.18(m, 2H, AA'BB'), 7.29(m, 2H, AA'BB'), 7.55(d, J=8.5Hz, 1H), 8.46(dd, J=8.5, 2.0Hz, 1H), 8.84(d, J=2.0Hz, 1H)

m.p.: 161 - 163°C.

#### Example 2

5-[1,5-Bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoic acid



To 8.7 g of the 1,5-bis(4-methoxyphenyl)pyrazol-3-yl 3-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)]-4-

chlorophenyl ketone prepared in Example 1 were added 100 ml of 3 N hydrochloric acid and 36 ml of ethanol. After heating under reflux for 3 hours, the reaction mixture was cooled in an ice bath and the crystals thus formed were collected by filtration. These crystals were washed into a flask with 60 ml of ethanol and 20 ml of 5 N sodium hydroxide and the resulting mixture was stirred overnight at room temperature. Then the mixture was heated under reflux for 3 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The crystals thus formed were collected by filtration and successively washed with a small amount of water and a small amount of ether. Water was added to these crystals and then 3 N hydrochloric acid was added thereto to acidify, followed by the extraction with ethyl acetate. The organic phase was washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After filtering, the filtrate was distilled to remove the solvent. The residue was recrystallized from toluene to give 5.2 g of the title compound in the form of white crystals.

NMR(CDCl<sub>3</sub>) $\delta$ :

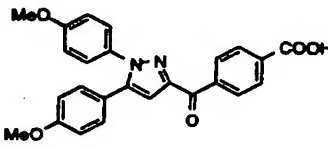
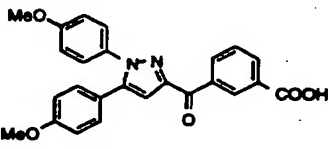
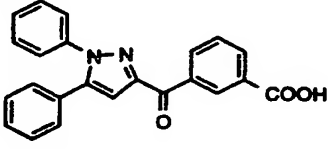
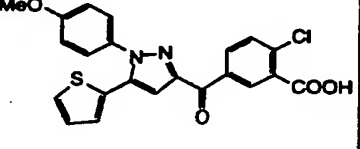
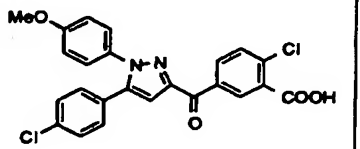
3.82(s, 3H), 3.83(s, 3H), 6.85(m, 2H, AA'BB'),  
6.89(m, 2H, AA'BB), 7.13(s, 1H), 7.18(m, 2H,

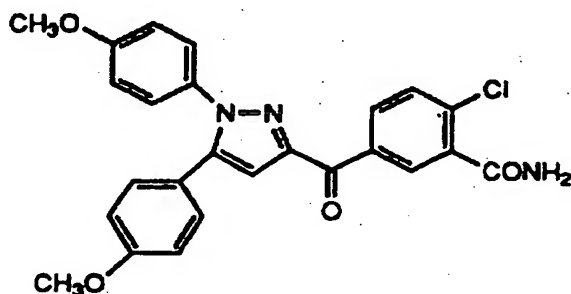
AA'BB'), 7.27(m, 2H, AA'BB'), 7.60(d, J=8.5Hz, 1H), 8.50(dd, J=8.5, 2.0Hz, 1H), 9.05(d, J=2.0Hz, 1H)

m.p.: 173 - 176°C.

The compounds described in the following Table 2 were prepared in the similar manner as that of Example 2.

Table 2

Ex.no.	Chemical formula	NMR data
3		NMR(CDCl <sub>3</sub> ) $\delta$ 3.81(s, 3H), 3.82(s, 3H), 6.86(m, 2H, AA'BB'), 6.89(m, 2H, AA'BB'), 7.14(s, 1H), 7.18(m, 2H, AA'BB'), 7.28(m, 2H, AA'BB'), 8.20(m, 2H, AA'BB'), 8.41(m, 2H, AA'BB')
4		NMR(CDCl <sub>3</sub> ) $\delta$ 3.80(s, 6H), 6.86(m, 2H, AA'BB'), 6.89(m, 2H, AA'BB'), 7.14(s, 1H), 7.20(m, 2H, AA'BB'), 7.30(m, 2H, AA'BB'), 7.62(t, J=8.0Hz, 1H), 8.31(dt, J=8.0, 0.5Hz, 1H), 8.59(dt, J=8.0, 0.5Hz, 1H), 9.08(t, J=0.5Hz, 1H)
5		NMR(CDCl <sub>3</sub> ) $\delta$ 7.05-7.60(m, 12H), 8.27(m, 1H), 8.44(m, 1H), 9.12(m, 1H).
6		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.55(s, 3H), 3.83(s, 3H), 7.05-7.10(m, 3H), 7.24(dd, J=4.0, 1.0Hz, 1H), 7.38(s, 1H), 7.45(m, 2H, AA'BB'), 7.60(dd, J=4.0, 1.0Hz, 1H), 7.73(d, J=8.5Hz, 1H), 8.40(dd, J=8.5, 2.0Hz, 1H), 8.58(d, J=2.0Hz, 1H)
7		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.77(s, 3H), 7.00(m, 2H, AA'BB'), 7.27(s, 1H), 7.30(m, 2H, AA'BB'), 7.31(m, 2H, AA'BB'), 7.44(m, 2H, AA'BB'), 7.56(d, J=8.4Hz, 1H), 8.21(dd, J=8.4, 2.2Hz, 1H), 8.41(d, J=2.2Hz, 1H)

Example 85-[1,5-Bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzamide

To 4.3 g (9.29 mmol) of 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoic acid were added 15.5 ml (11.1 mmol) of triethylamine and 45 ml of tetrahydrofuran and the obtained mixture was stirred in an ice-bath. Next, 1.0 ml (10.5 mmol) of ethyl chloroformate was added thereto and the resulting mixture was stirred at the ice temperature for 30 minutes. After blowing an ammonia gas into this solution at room temperature for 5 minutes, the mixture was stirred at room temperature for 1.5 hours. Then the reaction mixture was poured into 200 ml of water under vigorously stirring. The crystals thus formed were collected by filtration and successively washed with water and ether. Then the crystals were air-dried to thereby give 3.60 g of the title compound in the form of white crystals.

NMR(CDCl<sub>3</sub>) $\delta$ :

3.81(s, 3H), 3.82(s, 3H), 5.88(bs, 1H), 6.35(bs, 1H), 6.84(m, 2H, AA'BB'), 6.89(m, 2H, AA'BB'), 7.11(s, 1H), 7.17(m, 2H, AA'BB'), 7.26(m, 2H, AA'BB'), 7.54(d, J=8.5Hz, 1H), 8.40(bd, J=8.5Hz, 1H), 8.77(bs, 1H)

m.p.: 205 - 207°C.

The compounds described in the following Tables 3 and 4 were prepared in the similar manner as that of Example 8.



Table 3

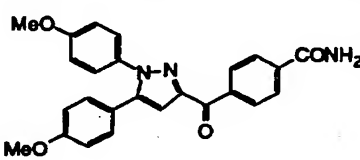
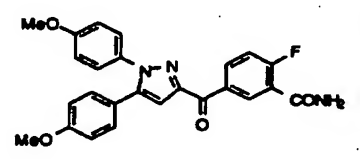
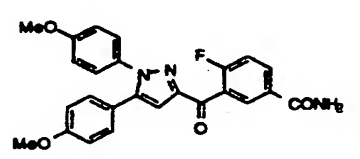
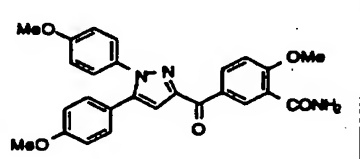
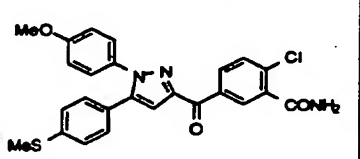
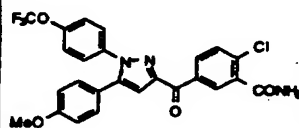
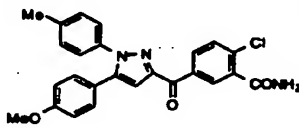
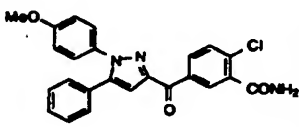
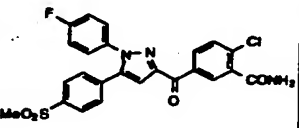
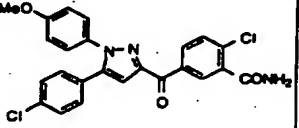
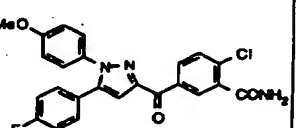
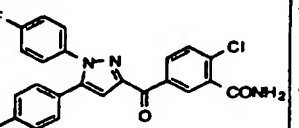
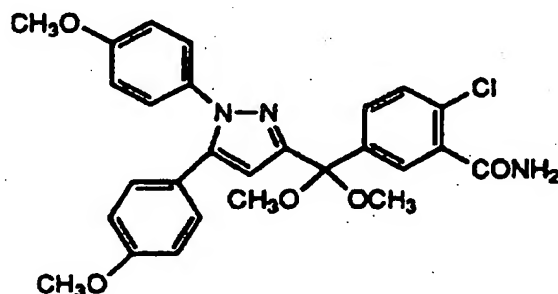
Ex.no.	Chemical formula	NMR data
9		NMR (CDCl <sub>3</sub> ) δ 3.80 (s, 3H), 3.82 (s, 3H), 6.86 (m, 2H, AA'BB'), 6.89 (m, 2H, AA'BB'), 7.13 (s, 1H), 7.18 (m, 2H, AA'BB'), 7.27 (m, 2H, AA'BB'), 7.92 (m, 2H), 8.43 (m, 2H)
10		NMR (CDCl <sub>3</sub> ) δ 3.82 (s, 6H), 5.85 (bs, 1H), 6.66 (bs, 1H), 6.85 (m, 2H, AA'BB'), 6.88 (m, 2H, AA'BB'), 7.12 (s, 1H), 7.18 (m, 2H, AA'BB'), 7.26 (t, J=9.0Hz, 1H), 7.30 (m, 2H, AA'BB'), 8.49 (ddd, J=9.0, 7.0, 2.5Hz, 1H), 9.22 (dd, J=7.0, 2.5Hz, 1H)
11		NMR (CDCl <sub>3</sub> ) δ 3.90 (s, 3H), 3.91 (s, 3H), 6.85 (m, 4H), 7.08 (s, 1H), 7.16 (m, 2H, AA'BB'), 7.22 (m, 2H, AA'BB'), 7.24 (t, J=8.5Hz, 1H), 8.02 (ddd, J=8.5, 5.5, 2.5Hz, 1H), 8.25 (dd, J=5.5, 2.5Hz, 1H)
12		NMR (DMSO-d <sub>6</sub> ) δ 3.74 (s, 3H), 3.78 (s, 3H), 3.96 (s, 3H), 6.92 (m, 2H, AA'BB'), 7.00 (m, 2H, AA'BB'), 7.12 (s, 1H), 7.22 (m, 2H, AA'BB'), 7.28 (d, J=9.0Hz, 1H), 7.31 (m, 2H, AA'BB'), 7.62 (bs, 1H), 7.70 (bs, 1H), 8.50 (dd, J=9.0, 2.5Hz, 1H), 8.69 (d, J=2.5Hz, 1H)
13		NMR (CDCl <sub>3</sub> ) δ 2.49 (s, 3H), 3.84 (s, 3H), 5.85 (bs, 1H), 6.33 (bs, 1H), 6.90 (m, 2H, AA'BB'), 7.13-7.20 (m, 4H), 7.16 (s, 1H), 7.25- 7.30 (m, 2H), 7.56 (d, J=8.5Hz, 1H), 8.42 (dd, J=8.5, 2.5Hz, 1H), 8.80 (d, J=2.5Hz, 1H)

Table 4

Ex.no.	Chemical formula	NMR data
14		NMR(CDCl <sub>3</sub> ) $\delta$ 3.83(s, 3H), 5.86(bs, 1H), 6.35(bs, 1H), 6.88(m, 2H, AA'BB'), 7.13(s, 1H), 7.17(m, 2H, AA'BB'), 7.23(m, 2H), 7.40(m, 2H), 7.57(d, J=8.5Hz, 1H), 8.39(dd, J=8.5, 2.5Hz, 1H), 8.83(d, J=2.5Hz, 1H).
15		NMR(CDCl <sub>3</sub> ) $\delta$ 2.35(s, 3H), 3.79(s, 3H), 6.14(bs, 1H), 6.58(bs, 1H), 6.82(m, 2H, AA'BB'), 7.08 (s, 1H), 7.14(m, 4H), 7.20(m, 2H), 7.52 (d, J=8.5Hz, 1H), 8.39(dd, J=8.5, 2.5Hz, 1H), 8.69(d, J=2.5Hz, 1H).
16		NMR(CDCl <sub>3</sub> +DMSO-d <sub>6</sub> ) $\delta$ 3.77(s, 3H), 6.26(bs, 1H), 6.70(bs, 1H), 6.83(m, 2H, AA'BB'), 7.11(s, 1H), 7.18- 7.31(m, 7H), 7.50(d, J=8.5Hz, 1H), 8.36(dd, J=8.5, 2.5Hz, 1H), 8.65(d, J=2.5Hz, 1H).
17		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.25(s, 3H), 7.35(t, J=8.6Hz, 2H), 7.46(s, 1H), 7.48-7.52(m, 2H, AA'BB'), 7.57(m, 2H, AA'BB'), 7.69(m, 2H, AA'BB'), 7.72(bs, 1H), 7.92(m, 2H, AA'BB'), 8.04(bs, 1H), 8.22(bs, 1H), 8.33(bd, J=8.4Hz, 1H).
18		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.78(s, 3H), 7.01(m, 2H, AA'BB'), 7.31(s, 1H), 7.30-7.34(m, 4H), 7.45(m, 2H, AA'BB'), 7.68(d, J=8.5Hz, 1H), 7.70(bs, 1H), 8.03(bs, 1H), 8.23 (d, J=2.2Hz, 1H), 8.32(dd, J=8.5, 2.2Hz, 1H).
19		NMR(CDCl <sub>3</sub> ) $\delta$ 3.78(s, 3H), 6.32(bs, 1H), 6.70(bs, 1H), 6.84(m, 2H, AA'BB'), 6.98(m, 2H), 7.08(s, 1H), 7.17(m, 2H), 7.19(m, 2H, AA'BB'), 7.49(d, J=8.5Hz, 1H), 8.35(dd, J=8.5, 2.5Hz, 1H), 8.64(d, J=2.5Hz, 1H).
20		NMR(CDCl <sub>3</sub> ) $\delta$ 6.35(bs, 1H), 6.73(bs, 1H), 6.99(m, 2H), 7.03(m, 2H), 7.09(s, 1H), 7.17(m, 2H), 7.26(m, 2H), 7.50(d, J=8.5Hz, 1H), 8.33(dd, J=8.5, 2.5Hz, 1H), 8.64(d, J=2.5Hz, 1H).

Example 21

5-[1-[1.5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1.1-dimethoxymethyl]-2-chlorobenzamide



To 3.60 g (7.79 mmol) of the 5-[1.5-bis-(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzamide prepared in Example 8 were added 72 ml of methanol, 8.5 ml (78 mmol) of trimethyl orthoformate and 1.48 g (7.79 mmol) of p-toluenesulfonic acid monohydrate and the obtained mixture was heated under reflux for 3 hours. After cooling, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate and concentrated. 100 ml of water was added to the concentrated reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After filtering, the filtrate was distilled to remove the solvent. The residue was recrystallized from ether to thereby give

2.3 g of the title compound in the form of white crystals. When analyzed by the powder X-ray diffraction method, these crystals were found to be converted into white amorphous powder by fine grinding.

NMR(CDCl<sub>3</sub>) $\delta$ :

3.26(s, 6H), 3.78(s, 3H), 3.79(s, 3H), 5.90(bs, 1H), 6.27(bs, 1H), 6.40(s, 1H), 6.78(m, 2H, AA'BB'), 6.80(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.16(m, 2H, AA'BB'), 7.39(d, J=8.4Hz, 1H), 7.68(dd, J=8.4, 2.3Hz, 1H), 8.07(d, J=2.3Hz, 1H)

m.p.: 93 - 95°C.

The compounds described in the following Tables 5 to 7 were prepared in the similar manner as that of Example 21.

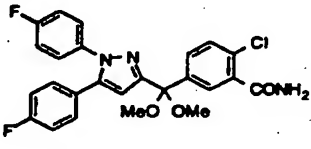
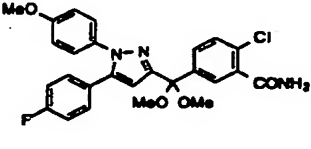
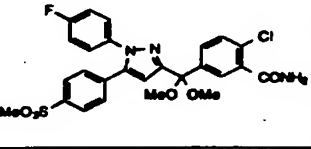
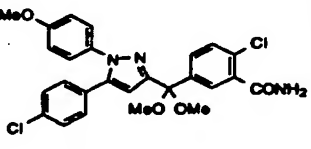
Table 5

Ex.no.	Chemical formula	NMR data
22		NMR(CDCl <sub>3</sub> ) $\delta$ 3.20(s, 6H), 3.70(s, 3H), 3.71(s, 3H), 6.32(s, 1H), 6.71(m, 2H, AA'BB'), 6.74(m, 2H, AA'BB'), 7.02(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.39(t, J=7.5Hz, 1H), 7.76(tt, J=7.5, 0.5Hz, 2H), 8.03(t, J=0.5Hz, 1H).
23		NMR(CDCl <sub>3</sub> ) $\delta$ 3.26(s, 6H), 3.76(s, 3H), 3.78(s, 3H), 5.80(bs, 1H), 6.38(s, 1H), 6.65(bs, 1H), 6.77(m, 2H, AA'BB'), 6.81(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.10(t, J=9.0Hz, 1H), 7.16(m, 2H, AA'BB'), 7.83(ddd, J=9.0, 7.0, 2.5Hz, 1H), 8.40(dd, J=7.0, 2.5Hz, 1H)
24		NMR(CDCl <sub>3</sub> ) $\delta$ 3.78(s, 3H), 3.79(s, 3H), 4.05(m, 2H), 4.25(m, 2H), 5.82(bs, 1H), 6.34(bs, 1H), 6.42(s, 1H), 6.78(m, 2H, AA'BB'), 6.80(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.16(m, 2H, AA'BB'), 7.42(d, J=8.5Hz, 1H), 7.73(dd, J=9.5, 2.5Hz, 1H), 8.06(d, J=2.5Hz, 1H)
25		NMR(CDCl <sub>3</sub> ) $\delta$ 1.77-1.93(m, 2H), 3.77(s, 3H), 3.79(s, 3H), 4.06(m, 2H), 4.25(m, 2H), 5.92(bs, 1H), 6.3(bs, 1H), 6.43(s, 1H), 6.78(m, 2H, AA'BB'), 6.81(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.17(m, 2H, AA'BB'), 7.42(d, J=8.5Hz, 1H), 7.72(dd, J=8.5, 2.5Hz, 1H), 8.03(d, J=2.5Hz, 1H)
26		NMR(CDCl <sub>3</sub> ) $\delta$ 3.24(s, 6H), 3.75(s, 3H), 3.77(s, 3H), 3.93(s, 3H), 6.35(s, 1H), 6.74(m, 2H, AA'BB'), 6.78(m, 2H, AA'BB'), 6.95(d, J=8.5Hz, 1H), 7.06(m, 2H, AA'BB'), 7.16(m, 2H, AA'BB'), 7.68(bs, 1H), 7.68(bs, 1H), 7.79(dd, J=8.5, 2.5Hz, 1H), 8.46(d, J=2.5Hz, 1H)
27		NMR(CDCl <sub>3</sub> ) $\delta$ 2.45(s, 3H), 3.26(s, 6H), 3.79(s, 3H), 5.92(bs, 1H), 6.31(bs, 1H), 6.44(s, 1H), 6.81(m, 2H, AA'BB'), 7.07(m, 2H, AA'BB'), 7.11(m, 2H, AA'BB'), 7.16(m, 2H, AA'BB'), 7.39(d, J=8.5Hz, 1H), 7.67(dd, J=8.5, 2.5Hz, 1H), 8.06(d, J=2.5Hz, 1H).

Table 6.

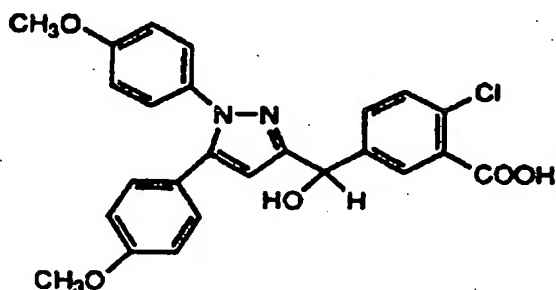
Ex.no.	Chemical formula	NMR data
28		NMR(CDC13)δ 3.16(s, 6H), 3.70(s, 6H), 5.66(bs, 1H), 6.59(s, 1H), 6.73(m, 4H), 6.98(m, 2H, AA'BB'), 7.03(m, 2H, AA'BB'), 7.29(d, J=8.5Hz, 1H), 7.38(dd, J=8.5, 2.0Hz, 1H), 7.61(d, J=2.0Hz, 1H), 8.49(bs, 1H)
29		NMR(CDC13)δ 3.26(s, 6H), 3.80(s, 3H), 5.90(bs, 1H), 6.30(bs, 1H), 6.42(s, 1H), 6.81(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.14(m, 2H), 7.29(m, 2H), 7.40(d, J=8.5Hz, 1H), 7.68(dd, J=8.5, 2.5Hz, 1H), 8.07(d, J=2.5Hz, 1H).
30		NMR(CDC13)δ 2.33(s, 3H), 3.26(s, 6H), 3.78(s, 3H), 5.83(bs, 1H), 6.31(bs, 1H), 6.40(s, 1H), 6.78(m, 2H, AA'BB'), 7.06-7.14(m, 6H), 7.39(d, J=8.5Hz, 1H), 7.67(dd, J=8.5, 2.5Hz, 1H), 8.60(d, J=2.5Hz, 1H).
31		NMR(DMSO-d6)δ 3.14(s, 6H), 3.78(s, 3H), 6.74(s, 1H), 6.98(m, 2H, AA'BB'), 7.00(d, J=3.6Hz, 1H), 7.05(dd, J=1.2, 3.6Hz, 1H), 7.22(m, 2H, AA'BB'), 7.43-7.49(m, 2H), 7.50(d, J=1.2Hz, 1H), 7.52(bs, 1H), 7.62(bs, 1H), 7.91(bs, 1H)
32		NMR(CDC13)δ 2.50(s, 3H), 3.27(s, 6H), 3.78(s, 3H), 3.80(s, 3H), 5.63(bs, 1H), 6.02(bs, 1H), 6.39(s, 1H), 6.78(m, 2H, AA'BB'), 6.81(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.17(m, 2H, AA'BB'), 7.23(d, 1H, J=8.0Hz), 7.59(dd, 1H, J=8.0, 2.0Hz), 7.83(d, 1H, J=2.0Hz)
33		NMR(CDC13)δ 1.26(t, 6H, J=7.2Hz), 3.44(q, 2H, J=7.2Hz), 3.53(q, 2H, J=7.2Hz), 3.29(s, 6H), 5.80(bs, 1H) 6.35(bs, 1H), 6.51(s, 1H), 6.78(m, 2H, AA'BB'), 6.80(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.14 (m, 2H, AA'BB'), 7.37(d, 1H, J=8.4Hz), 7.68(dd, 1H, J=8.4, 2.0Hz), 8.07(d, 1H, J=2.0Hz)
34		NMR(DMSO-d6)δ 3.16(s, 6H), 3.71(s, 3H), 3.73(s, 3H), 6.60(s, 1H), 6.86(m, 2H, AA'BB'), 6.90(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.12(m, 2H, AA'BB'), 7.41(d, J=7.5Hz, 1H), 7.46(d, J=7.5, 1.5Hz, 1H), 7.56(d, J=1.5Hz, 1H), 7.57(bs, 1H), 7.87(bs, 1H)

Table 7

Ex.no.	Chemical formula	NMR data
35		NMR (DMSO-d <sub>6</sub> ) δ 3.16 (s, 6H), 6.70 (s, 1H), 7.15-7.28 (m, 8H), 7.45 (d, J=8.5Hz, 1H), 7.51 (dd, J=8.5, 2.5Hz, 1H), 7.54 (d, J=2.5Hz, 1H), 7.62 (bs, 1H), 7.91 (bs, 1H).
36		NMR (DMSO-d <sub>6</sub> ) δ 3.16 (s, 6H), 3.72 (s, 3H), 6.67 (s, 1H), 6.91 (m, 2H, AA'BB'), 7.10 (m, 2H, AA'BB'), 7.16 (m, 2H), 7.24 (m, 2H), 7.45 (d, J=8.5Hz, 1H), 7.51 (dd, J=8.5, 2.5Hz, 1H), 7.54 (d, J=2.5Hz, 1H), 7.61 (bs, 1H), 7.90 (bs, 1H).
37		NMR (DMSO-d <sub>6</sub> ) δ 3.17 (s, 6H), 3.22 (s, 3H), 6.88 (s, 1H), 7.22- 7.31 (m, 4H), 7.40-7.50 (m, 3H), 7.52 (d, J=2.2Hz, 1H), 7.55 (m, 1H), 7.63 (bs, 1H), 7.87 (m, 2H), 7.92 (bs, 1H).
38		NMR (DMSO-d <sub>6</sub> ) δ 3.16 (s, 6H), 3.74 (s, 3H), 6.72 (s, 1H), 6.92 (m, 2H, AA'BB'), 7.12 (m, 2H, AA'BB'), 7.22 (m, 2H, AA'BB'), 7.38 (m, 2H, AA'BB'), 7.45 (bd, J=8.4Hz, 1H), 7.51 (bd, J=8.4Hz, 1H), 7.54 (bs, 1H), 7.63 (bs, 1H), 7.92 (bs, 1H).

Example 39

(±)-5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1-hydroxymethyl]-2-chlorobenzoic acid



3.82 g (16.2 mmol) of 2-chloro-5-bromobenzoic acid was dissolved in 30 ml of dry tetrahydrofuran and 20.3 ml (32.5 mmol) of a 1.6 M solution of n-butyl-lithium in hexane was dropwise added thereto in a nitrogen atmosphere at  $-100^{\circ}\text{C}$ . The resulting mixture was stirred at  $-100^{\circ}\text{C}$  for 30 minutes and then at  $-78^{\circ}\text{C}$  for 2 hours. Subsequently, a solution of 5.0 g (16.2 mmol) of 1,5-bis(4-methoxyphenyl)-3-pyrazole-carbaldehyde in dry tetrahydrofuran (30 ml) was dropwise added thereto. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 hour and then slowly heated to room temperature. After stirring at room temperature overnight, 200 ml of water was added to the reaction mixture, and then diluted hydrochloric acid was added thereto to thereby make the aqueous phase acidic. The resulting mixture was extracted with ethyl acetate.



The organic phase was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. After filtering, the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate) to thereby give 4.30 g of the title compound as pale yellow amorphous powder.

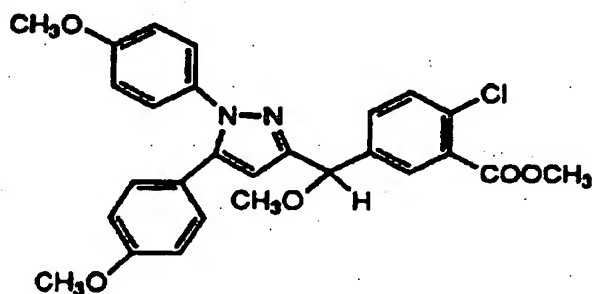
NMR(CDCl<sub>3</sub>) $\delta$ :

3.70(s, 3H), 3.80(s, 3H), 6.00(s, 1H), 6.25(s, 1H), 6.78(m, 2H, AA'BB'), 6.83(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.43(d, J=9.0Hz, 1H), 7.59(dd, J=9.0, 1.5Hz, 1H), 8.14(d, J=1.5Hz, 1H)

The compounds described in the following Table 8 were prepared in the similar manner as that of Example 39.

Table 8.

Ex.no.	Chemical formula	NMR data
40		NMR (CDCl <sub>3</sub> ) δ 3.71 (s, 3H), 3.74 (s, 3H), 5.67 (s, 1H), 6.40 (s, 1H), 6.86 (m, 2H, AA'BB'), 6.91 (d, J=8.5Hz, 1H), 6.92 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.12 (m, 2H, AA'BB'), 7.58 (dd, J=8.5, 2.5Hz, 1H), 7.89 (d, J=2.5Hz, 1H)
41		NMR (CDCl <sub>3</sub> ) δ 3.76 (s, 3H), 3.80 (s, 3H), 6.03 (s, 1H), 7.20 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.85 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'), 7.48 (bt, J=8.0Hz, 1H), 7.80 (d, J=8.0Hz, 1H), 8.01 (d, J=8.0Hz, 1H), 8.28 (bs, 1H).
42		NMR (CDCl <sub>3</sub> ) δ 3.76 (s, 2H), 6.03 (s, 1H), 6.21 (s, 1H), 6.76 (m, 2H), 7.07 (m, 2H), 7.18-7.36 (m, 5H), 7.44 (m, 1H), 7.77 (m, 1H), 8.00 (m, 1H), 8.29 (m, 1H).
43		NMR (CDCl <sub>3</sub> ) δ 6.02 (s, 1H), 6.28 (s, 1H), 7.13-7.17 (m, 2H), 7.21-7.35 (m, 8H), 7.44 (m, 1H), 7.76 (m, 1H), 7.99 (m, 1H), 8.24 (m, 1H).
44		NMR (CDCl <sub>3</sub> ) δ 2.44 (s, 3H), 3.82 (s, 3H), 6.05 (bs, 1H), 6.23 (s, 1H), 6.87 (m, 2H, AA'BB'), 7.07 (m, 2H, AA'BB'), 7.11 (m, 2H, AA'BB'), 7.22 (m, 2H, AA'BB'), 7.49 (m, 1H), 7.80 (m, 1H), 8.04 (m, 1H), 8.29 (m, 1H).

Example 45Methyl (+)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoate

4.30 g (4.3 mmol) of the (+)-5-[1-[1,5-bis-(4-methoxyphenyl)pyrazol-3-yl]-1-hydroxymethyl]-2-chlorobenzoic acid prepared in Example 39 was dissolved in 3 ml of N,N-dimethylformamide and the resulting solution was stirred at room temperature. Then 0.36 g (9.0 mmol) of 60% sodium hydride and 0.8 ml (12.8 mmol) of methyl iodide were added to the solution and the resulting mixture was stirred at 50°C for 2 hours. To the reaction mixture were carefully added 100 ml of ethyl acetate and 30 ml of water and then the ethyl acetate phase was separated therefrom. The aqueous phase was extracted with ethyl acetate. Then the organic phases (ethyl acetate phases) were combined, washed with saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After filtering, the filtrate was distilled to remove

ethyl acetate. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate) to thereby give 1.5 g of the title compound as pale yellow oily substance.

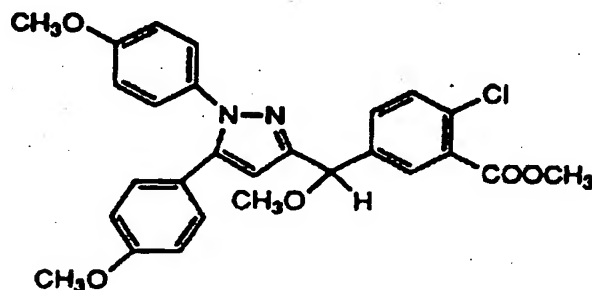
NMR(CDCl<sub>3</sub>) $\delta$ :

3.45(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 3.91(s, 3H), 5.42(s, 1H), 6.24(s, 1H), 6.77(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.19(m, 2H, AA'BB'), 7.44(d, J=9.0Hz, 1H), 7.58(bd, J=9.0Hz, 1H), 7.99(bs, 1H)

Example 46

Methyl (+)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoate

Methyl (-)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoate



1.90 g of the methyl (+)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoate prepared in Example 45 was dissolved in solvent mixture comprising n-hexane and ethanol (4 : 6). The

resulting solution was injected into a CHIRALCEL OJ column [25 cm x 2 cm (i.d.), mfd. by Daicel Chemical Industries, Ltd.] in 16 portions (flow rate: 20 ml/min) to thereby purify each enantiomer (eluted with n-hexane/ethanol = 4 : 6). Thus, 0.70 g of the (+) enantiomer of the title compound was eluted prior to the elution of 0.70 g of the (-) one.

Specific rotation

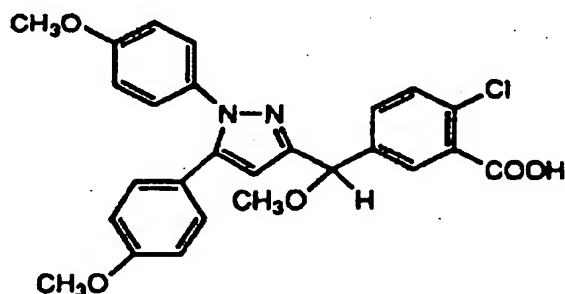
(+) enantiomer:  $[\alpha]_D^{24} + 52.2^\circ$  (c1.02,  $\text{CHCl}_3$ )

(-) enantiomer:  $[\alpha]_D^{24} - 47.2^\circ$  (c1.10,  $\text{CHCl}_3$ ).

Example 47

(+)-5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoic acid

(-)-5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoic acid



0.23 g (0.50 mmol) of the methyl (+)-5-[[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]methoxymethyl]-2-chlorobenzoate prepared in Example 46 was dissolved in 30 ml of mixture of methanol and water (3 : 1). Then

1 ml of 5 N solution of sodium hydroxide was added to the resulting solution and the obtained mixture was stirred at 40°C for 1.5 hours. After cooling, the pH of the reaction mixture was adjusted to 1 with 1 N hydrochloric acid. Next, the mixture was extracted with dichloromethane. The organic phase was washed with saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After filtering, the filtrate was distilled to remove the solvent. Thus, 0.21 g of (+)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoic acid was obtained as white amorphous powder.

NMR(CDCl<sub>3</sub>) $\delta$ :

3.46(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 5.50(s, 1H), 6.35(s, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.21(m, 2H, AA'BB'), 7.46(d, J=9.0Hz, 1H), 7.62(dd, J=9.0, 2.5Hz, 1H), 8.13(d, J=2.5Hz, 1H)

Specific rotation:  $[\alpha]_D^{24} + 41.3^\circ$  (c1.05, CHCl<sub>3</sub>).

Similarly, 0.21 g of (-)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoic acid was obtained as white amorphous powder from 0.23 g (0.50 mmol) of the methyl (-)-5-[1-[1,5-bis-(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoate prepared in Example 46.

Specific rotation:  $[\alpha]_D^{24} - 41.0^\circ$  (c1.00,  $\text{CHCl}_3$ ).

The compounds described in the following Tables 9 and 10 were prepared in the similar manner as that of Example 47.

Table 9

Ex.no.	Chemical formula	NMR data
48		NMR(CDCl <sub>3</sub> ) $\delta$ 3.46(s, 3H), 3.80(s, 3H), 5.50(s, 1H), 6.40(s, 1H), 6.85(m, 2H, AA'BB'), 7.11(m, 2H, AA'BB'), 7.19(m, 2H, AA'BB'), 7.23 (m, 2H, AA'BB'), 7.47(d, J=8.5Hz, 1H), 7.62(dd, J=8.5, 1.0Hz, 1H), 8.13(d, J=1.0Hz, 1H)
49		NMR(CDCl <sub>3</sub> ) $\delta$ 3.42(s, 3H), 3.78(s, 3H), 5.47(s, 1H), 6.34(s, 1H) 6.83(m, 2H), 7.07(m, 1H) 7.12-7.28(m, 4H) 7.41(m, 1H), 7.72(m, 1H), 7.99(m, 1H), 8.26(m, 1H).
50		NMR(CDCl <sub>3</sub> ) $\delta$ 3.47(s, 3H), 3.79(s, 3H), 5.52(s, 1H), 6.38(s, 1H), 6.83(m, 2H), 7.14-7.28(m, 6H), 7.47(m, 1H), 7.78(m, 1H), 8.03(m, 1H), 8.29(m, 1H).
51		NMR(CDCl <sub>3</sub> ) $\delta$ 3.45(s, 3H), 3.78(s, 3H), 3.82(s, 3H), 4.09(s, 3H), 5.43(s, 1H), 6.30(s, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.08(d, J=8.5Hz, 1H), 7.09(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.78(dd, J=8.5, 2.5Hz, 1H), 8.34(d, J=2.5Hz, 1H)
52		NMR(CDCl <sub>3</sub> ) $\delta$ 2.32(s, 3H), 3.35(s, 3H), 3.67(s, 3H), 3.73(s, 3H), 5.53(s, 1H), 6.15(s, 1H), 6.65(m, 2H, AA'BB'), 6.76(m, 2H, AA'BB'), 6.97(m, 2H, AA'BB'), 7.10, (d, J=8.5Hz, 1H), 7.11(m, 2H, AA'BB'), 7.81(dd, J=8.5, 2.5Hz, 1H), 8.35(d, J=2.5Hz, 1H)
53		NMR(CDCl <sub>3</sub> ) $\delta$ 3.32(s, 3H), 3.71(s, 3H), 3.74(s, 3H), 5.41(s, 1H), 6.44(s, 1H), 6.85(m, 2H, AA'BB'), 6.92(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.15(m, 2H, AA'BB'), 7.35(bd, J=9.0Hz, 1H), 7.53(bd, J=9.0Hz, 1H), 7.81(bs, 1H)
54		NMR(CDCl <sub>3</sub> ) $\delta$ 3.46(s, 3H), 3.76(s, 3H), 3.80(s, 3H), 5.50(s, 1H), 6.30(s, 3H), 6.77(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.21(m, 2H, AA'BB'), 7.48(t, J=8.0Hz, 1H), 7.79(bd, J=8.0Hz, 1H), 8.02(dt, J=8.0, 0.5Hz, 1H), 8.27(t, J=0.5Hz, 1H)



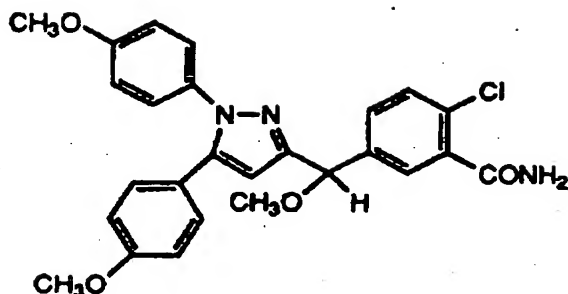
Table 10

Ex.no.	Chemical formula	NMR data
55		NMR(CDCl <sub>3</sub> ) $\delta$ 3.47(s, 3H), 3.79(s, 3H), 5.50(s, 1H), 6.33(s, 1H), 6.80(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.24(m, 2H, AA'BB'), 7.29(m, 2H, AA'BB'), 7.49(m, 1H), 7.78(m, 1H), 8.04(m, 1H), 8.27(m, 1H).
56		NMR(CDCl <sub>3</sub> ) $\delta$ 3.48(s, 3H), 5.54(s, 1H), 6.40(s, 1H), 7.16-7.21(m, 2H), 7.23-7.35(m, 8H), 7.49(m, 1H), 7.80(m, 1H), 8.04(m, 1H), 8.29(m, 1H).
57		NMR(CDCl <sub>3</sub> ) $\delta$ 2.44(s, 3H), 3.47(s, 3H), 3.80(s, 3H), 5.52(s, 1H), 6.36(m, 2H), 6.85(m, 2H, AA'BB'), 7.07(m, 2H, AA'BB'), 7.11(m, 2H, AA'BB'), 7.22(m, 2H, AA'BB'), 7.48(m, 1H), 7.79(m, 1H), 8.04(m, 1H), 8.28(m, 1H).
58		NMR(CDCl <sub>3</sub> ) $\delta$ 3.49(s, 3H), 3.76(s, 3H), 3.79(s, 3H), 5.78(s, 1H), 6.38(s, 1H), 6.78(m, 2H, AA'BB'), 6.83(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.14(t, J=9.0Hz, 1H), 7.22(m, 2H, AA'BB'), 8.06(ddd, J=9.0, 6.0, 2.5Hz, 1H), 8.45(dd, J=6.0, 2.5Hz, 1H).
59		NMR(CDCl <sub>3</sub> ) $\delta$ 1.29(t, J=7.0Hz, 3H) 3.62(m, 2H), 3.78(s, 3H), 3.80(s, 3H), 5.61(s, 1H), 6.37(s, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.21(m, 2H, AA'BB'), 7.46(d, J=8.5Hz, 1H), 7.64(dd, J=8.5, 2.5Hz, 1H), 8.13(d, J=2.5Hz, 1H).

Example 60

(+)-5-[1-[1.5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzamide

(-)-5-[1-[1.5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzamide



0.21 g (0.44 mmol) of the (+)-5-[1-[1,5-bis-(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoic acid prepared in Example 47 was dissolved in 3 ml of N,N-dimethylformamide and the resulting solution was stirred at room temperature. To the obtained solution were added 73 mg (0.54 mmol) of N-hydroxy-benzotriazole and 83 ml (0.53 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and the obtained mixture was stirred at room temperature for 3 hours. After blowing ammonia gas into the mixture at room temperature for 5 minutes, the mixture was stirred at room temperature for 1.5 hours. Then 30 ml of water was added to the mixture, followed by the extraction with ethyl acetate. The organic phase was washed with saturated aqueous solution of sodium hydrogencarbonate and dried over magnesium sulfate. After filtering, the filtrate was distilled under reduced pressure to remove the solvent. The obtained residue was subjected to column chromatography by

using NAM200H silica gel (mfd. by Namu Kenkyusho; eluted with methanol/dichloromethane). Thus, 0.11 g of (+)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzamide was obtained as white amorphous powder.

NMR(CDCl<sub>3</sub>) $\delta$ :

3.46(s, 3H), 3.78(s, 3H), 3.81(s, 3H), 5.43(s, 1H), 6.19(bs, 1H), 6.28(s, 1H), 6.39(bs, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.19(m, 2H, AA'BB'), 7.42(d, J=8.5Hz, 1H), 7.57(dd, J=8.5, 2.5Hz, 1H), 8.14(d, J=2.5Hz, 1H)

Specific rotation:  $[\alpha]^{24}_D + 46.0^\circ$  (c1.01, CHCl<sub>3</sub>).

Similarly, (-)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzamide was obtained from the (-)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-chlorobenzoic acid prepared in Example 47.

Specific rotation:  $[\alpha]^{24}_D - 45.1^\circ$  (c1.01, CHCl<sub>3</sub>)

m.p.: 76 - 80°C.

The compounds described in the following Tables 11 to 13 were prepared in the similar manner as that of Example 60.

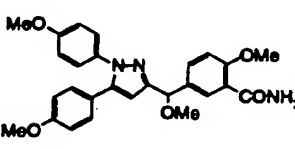
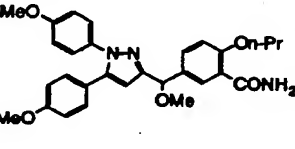
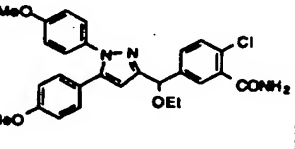
Table 11

Ex.no.	Chemical formula	NMR data
61		NMR(CDCl <sub>3</sub> ) $\delta$ 3.46(s, 3H), 3.76(s, 3H), 3.80(s, 3H), 5.49(s, 1H), 5.65(bs, 1H), 6.20(bs, 1H), 6.30(s, 1H), 6.78(m, 2H, AA'BB'), 6.83(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.46(t, J=8.5Hz, 1H), 7.70(d, J=8.5Hz, 1H), 7.78(d, J=8.5Hz, 1H), 7.95(s, 1H).
62		NMR(CDCl <sub>3</sub> ) $\delta$ 3.00(d, J=1.5Hz, 3H), 3.46(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 5.48(s, 1H), 6.20(bs, 1H), 6.27(s, 1H), 6.76(m, 2H, AA'BB'), 6.83(m, 2H, AA'BB'), 7.07(m, 2H, AA'BB'), 7.19(m, 2H, AA'BB'), 7.42(bt, J=8.0Hz, 1H), 7.63(bd, J=8.0Hz, 1H), 7.72(bd, J=8.0Hz, 1H), 7.84(bs, 1H).
63		NMR(CDCl <sub>3</sub> ) $\delta$ 3.47(s, 3H), 3.76(s, 3H), 3.80(s, 3H), 5.48(s, 1H), 5.71(bs, 1H), 6.10(bs, 1H), 6.27(s, 1H), 6.77(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.62(m, 2H, AA'BB'), 7.82(m, 2H, AA'BB').
64		NMR(CDCl <sub>3</sub> ) $\delta$ 3.46(s, 3H), 3.78(s, 3H), 3.81(s, 3H), 5.43(s, 1H), 6.19(bs, 1H), 6.28(s, 1H), 6.39(bs, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.19(m, 2H, AA'BB'), 7.42(d, J=8.5Hz, 1H), 7.57(dd, J=8.5, 2.5Hz, 1H), 7.91(d, J=2.5Hz, 1H).
65		NMR(CDCl <sub>3</sub> ) $\delta$ 2.45(s, 3H), 3.47(s, 3H), 3.80(s, 3H), 5.50(s, 1H), 6.31(s, 1H), 6.84(m, 2H, AA'BB'), 7.06(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.62(m, 2H, AA'BB'), 7.82(m, 2H, AA'BB').
66		NMR(CDCl <sub>3</sub> ) $\delta$ 3.03(s, 3H), 3.48(s, 3H), 3.83(s, 3H), 5.51(s, 1H), 5.55(bs, 1H), 6.06(bs, 1H), 6.43(s, 1H), 6.89(m, 2H, AA'BB'), 7.17(m, 2H, AA'BB'), 7.35(m, 2H, AA'BB'), 7.60(m, 2H, AA'BB'), 7.81(m, 2H, AA'BB'), 7.83(m, 2H, AA'BB').

Table 12

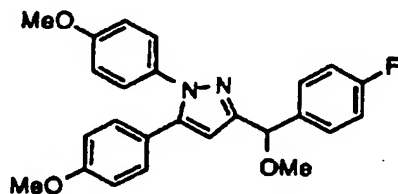
Ex.no.	Chemical formula	NMR data
67		NMR(CDC13)δ 3.42(s,3H), 3.80(s,3H), 5.42(s,1H), 5.91(bs,1H), 6.33(s,1H), 6.34(bs,1H), 6.84(m,2H,AA'BB'), 7.10(m,2H,AA'BB'), 7.17(m,2H,AA'BB'), 7.21(m,2H,AA'BB'), 7.41(bd,J=8.0Hz,1H), 7.57(bd,J=8.0Hz,1H), 7.80(bs,1H)
68		NMR(CDC13)δ 2.45(s,3H), 3.47(s,3H), 3.81(s,3H), 5.49(s,1H), 5.62(bs,1H), 6.19(bs,1H), 6.32 (s,1H), 6.85(m,2H,AA'BB'), 7.07(m,2H, AA'BB'), 7.11(m,2H,AA'BB'), 7.20(m,2H, AA'BB'), 7.47(m,1H), 7.70(m,1H), 7.78(m,1H), 7.96(m,1H).
69		NMR(CDC13)δ 3.47(s,3H), 3.77(s,3H), 3.80(s,3H), 5.43(s,1H), 6.27(s,1H), 6.32(bs,1H), 6.45(bs,1H), 6.78(m,2H,AA'BB'), 6.85(m,2H,AA'BB'), 7.09(m,2H,AA'BB'), 7.20(m,2H,AA'BB'), 7.49(d,J=8.0Hz,1H), 7.61(s,1H), 7.80(d,J=8.0Hz,1H)
70		NMR(CDC13)δ 3.44(s,3H), 3.77(s,3H), 3.80(s,3H), 3.97(s,3H), 5.43(s,1H), 5.77(bs,1H), 6.30(s,1H), 6.77(m,2H,AA'BB'), 6.83(m,2H,AA'BB'), 7.02(d,J=8.5Hz,1H), 7.08(m,2H,AA'BB'), 7.20(m,2H,AA'BB'), 7.69(dd,J=8.5,2.5Hz,1H), 7.72(bs,1H), 8.35(d,J=2.5Hz,1H)
71		NMR(CDC13)δ 3.50(s,3H), 3.77(s,3H), 3.80(s,3H), 5.77(s, 1H), 5.86(bs,1H), 6.29(bs,1H), 6.33(s,1H), 6.77(m,2H,AA'BB'), 6.83(m,2H,AA'BB'), 7.09(m,2H,AA'BB'), 7.13(t,J=9.0Hz,1H), 7.19(m,2H,AA'BB'), 7.84(ddd,J=9.0,6.0, 2.5Hz,1H), 8.13(dd,J=6.0,2.5Hz,1H)
72		NMR(CDC13)δ 3.50(s,3H), 3.77(s,3H), 3.80(s,3H), 5.77(s,1H), 5.86(bs,1H), 6.29(bs,1H), 6.33 (s,1H), 6.77(m,2H,AA'BB'), 6.83(m,2H, AA'BB'), 7.09(m,2H,AA'BB'), 7.13(t,J=9.0Hz, 1H), 7.19(m,2H,AA'BB'), 7.84(ddd,J=9.0,6.0,2.5Hz,1H), 8.13(dd,J=6.0,2.5Hz,1H)

Table 13

Ex.no.	Chemical formula	NMR data
73		NMR(CDC13) $\delta$ 3.44 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.97 (s, 3H), 5.43 (s, 1H), 5.77 (bs, 1H), 6.30 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.83 (m, 2H, AA'BB'), 7.02 (d, J=8.5Hz, 1H), 7.08 (m, 2H, AA'BB'), 7.20 (m, 2H, AA'BB'), 7.69 (dd, J=8.5, 2.5Hz, 1H), 7.72 (bs, 1H), 8.35 (d, J=2.5Hz, 1H)
74		NMR(CDC13) $\delta$ 1.09 (t, J=9.0Hz, 3H), 1.90 (qt, J=9.0, 9.0Hz, 2H), 3.43 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.10 (t, J=9.0Hz, 2H), 5.43 (s, 1H), 5.91 (bs, 1H), 6.30 (s, 1H), 6.76 (m, 2H, AA'BB'), 6.82 (m, 2H, AA'BB'), 6.99 (d, J=8.5Hz, 1H), 7.08 (m, 2H, AA'BB'), 7.19 (m, 2H, AA'BB'), 7.65 (dd, J=8.5, 2.5Hz, 1H), 8.35 (d, J=2.5Hz, 1H)
75		NMR(CDC13) $\delta$ 1.28 (t, J=7.0Hz, 3H), 3.61 (m, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 5.54 (s, 1H), 6.04 (bs, 1H), 6.30 (s, 1H), 6.35 (bs, 1H), 6.77 (m, 2H, AA'BB'), 6.84 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.19 (m, 2H, AA'BB'), 7.40 (d, j=8.5Hz, 1H), 7.58 (dd, J=8.5, 2.5Hz, 1H), 7.91 (d, J=2.5Hz, 1H).

Example 76

(±)-3-[1-(4-Fluorophenyl)-1-methoxymethyl]-1,5-bis-  
(4-methoxyphenyl)pyrazole



0.80 g (1.98 mmol) of the ( $\pm$ )-( $\alpha$ )-(4-fluorophenyl)-1,5-bis(4-methoxyphenyl)-3-pyrazolemethanol was dissolved in 3 ml of N,N-dimethylformamide and the resulting solution was stirred at room temperature. After adding 0.14 g (3.5 mmol) of 60% sodium hydride and 0.8 ml (12.9 mmol) of methyl iodide thereto, the resulting mixture was stirred at 40°C for 1 hour. 20 ml of water was added to the reaction mixture, followed by the extraction with ethyl acetate. The organic phase was washed with saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After filtering, the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate) to thereby give the title compound as colorless oily substance.

NMR(CDCl<sub>3</sub>) $\delta$ :

3.44(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 5.42(s, 1H), 6.29(s, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.03-7.08(m, 2H), 7.09(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.48-7.52(m, 2H)

The compounds described in the following Tables 14 to 17 were prepared in the similar manner as that of Example 76.

Table 14

Ex.no.	Chemical formula	NMR data
77		NMR(CDCl <sub>3</sub> ) $\delta$ 3.44 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 5.42 (s, 1H), 6.29 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.84 (m, 2H, AA'BB'), 7.03-7.08 (m, 2H), 7.09 (m, 2H, AA'BB'), 7.20 (m, 2H, AA'BB'), 7.48-7.52 (m, 2H)
78		NMR(CDCl <sub>3</sub> ) $\delta$ 3.45 (s, 3H), 3.81 (s, 3H), 5.44 (s, 1H), 6.36 (s, 1H), 6.85 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.18 (m, 2H, AA'BB'), 7.22 (m, 2H, AA'BB'), 7.30 (m, 1H), 7.39 (m, 2H), 7.53 (m, 2H).
79		NMR(CDCl <sub>3</sub> ) $\delta$ 3.47 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.43 (s, 1H), 6.29 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.85 (m, 2H, AA'BB'), 6.97 (m, 1H), 7.10 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'), 7.25-7.34 (m, 3H)
80		NMR(CDCl <sub>3</sub> ) $\delta$ 3.04 (s, 3H), 3.43 (s, 3H), 3.81 (s, 3H), 5.42 (s, 1H), 6.44 (s, 1H), 6.87 (m, 2H, AA'BB'), 7.04-7.10 (m, 2H), 7.17 (m, 2H, AA'BB'), 7.36 (m, 2H, AA'BB'), 7.46-7.52 (m, 2H), 7.82 (m, 2H, AA'BB')
81		NMR(CDCl <sub>3</sub> ) $\delta$ 3.44 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 5.48 (s, 1H), 6.36 (dd, J=3.0, 1.5Hz, 1H), 6.40 (d, J=3.0Hz, 1H), 6.59 (s, 1H), 6.80 (m, 2H, AA'BB'), 6.84 (m, 2H, AA'BB'), 7.14 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'), 7.45 (dd, J=1.5, 0.5Hz, 1H)
82		NMR(CDCl <sub>3</sub> ) $\delta$ 3.43 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 5.40 (s, 1H), 6.31 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.83 (m, 2H, AA'BB'), 6.91 (d, J=8.5Hz, 2H), 7.09 (m, 2H, AA'BB'), 7.20 (m, 2H, AA'BB'), 7.46 (d, J=8.5Hz, 2H)
83		NMR(CDCl <sub>3</sub> ) $\delta$ 3.48 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 5.50 (s, 1H), 6.27 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.85 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'), 7.62 (d, J=8.0Hz, 2H), 7.66 (d, J=8.0Hz, 2H)



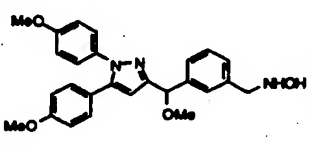
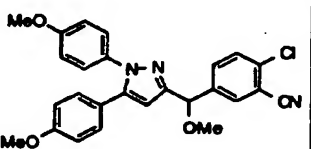
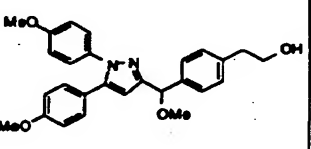
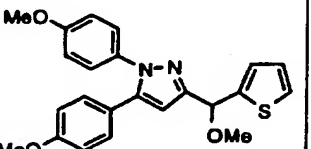
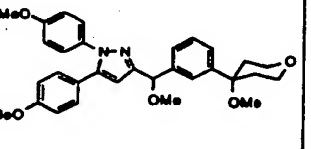
Table 15

Ex.no.	Chemical formula	NMR data
84		NMR(CDCl <sub>3</sub> ) $\delta$ 3.36(s, 3H), 3.72(s, 3H), 3.74(s, 3H), 5.94(s, 1H), 6.51(s, 1H), 6.74(m, 2H, AA'BB'), 6.75(m, 2H, AA'BB'), 7.04(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB')
85		NMR(CDCl <sub>3</sub> ) $\delta$ 3.48(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 5.49(s, 1H), 6.28(s, 1H), 6.78(m, 2H, AA'BB'), 6.85(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.21(m, 2H, AA'BB'), 7.48(t, J=7.5Hz, 1H), 7.55(d, J=7.5Hz, 1H), 7.70(d, J=7.5Hz, 1H), 7.82(s, 1H)
86		NMR(CDCl <sub>3</sub> ) $\delta$ 2.45(s, 3H), 3.46(s, 3H), 3.81(s, 3H), 5.43(s, 1H), 6.33(s, 1H), 6.85(m, 2H, AA'BB'), 6.98(bt, J=9.0Hz, 1H), 7.08(m, 2H, AA'BB'), 7.11(m, 2H, AA'BB'), 7.21(m, 2H, AA'BB'), 7.27-7.35(m, 3H)
87		NMR(CDCl <sub>3</sub> ) $\delta$ 2.45(s, 3H), 3.46(s, 3H), 3.81(s, 3H), 3.83(s, 3H), 5.42(s, 1H), 6.35(s, 1H), 6.82-6.87(m, 3H), 7.07(m, 2H, AA'BB'), 7.09-7.13(m, 4H), 7.21(m, 2H, AA'BB'), 7.29(t, J=8.0Hz, 1H)
88		NMR(CDCl <sub>3</sub> ) $\delta$ 3.05(s, 3H), 3.47(s, 3H), 3.83(s, 6H), 5.44(s, 1H), 6.47(s, 1H), 6.84-6.90(m, 3H), 7.12(bd, J=8.0Hz, 2H), 7.19(m, 2H, AA'BB'), 7.31(t, J=8.0Hz, 1H), 7.36(m, 2H, AA'BB'), 7.82(m, 2H, AA'BB')
89		NMR(CDCl <sub>3</sub> ) $\delta$ 3.04(s, 3H), 3.47(s, 3H), 3.83(s, 3H), 5.45(s, 1H), 6.45(s, 1H), 6.88(m, 2H, AA'BB'), 7.00(bt, J=9.0Hz, 1H), 7.18(m, 2H, AA'BB'), 7.24-7.34(m, 3H), 7.37(m, 2H, AA'BB'), 7.82(m, 2H, AA'BB')
90		NMR(CDCl <sub>3</sub> ) $\delta$ 3.56(s, 3H), 3.78(s, 3H), 3.81(s, 3H), 5.79(s, 1H), 6.41(s, 1H), 6.79(m, 2H, AA'BB'), 6.85(m, 2H, AA'BB'), 7.12(m, 2H, AA'BB'), 7.23(m, 2H, AA'BB'), 7.37(d, J=3.0Hz, 1H), 7.80(d, J=3.0Hz, 1H)

Table 16

Ex.no.	Chemical formula	NMR data
91		NMR(CDC13) $\delta$ 2.45(s, 3H), 3.46(s, 3H), 3.81(s, 3H), 5.45(s, 1H), 6.34(s, 1H), 6.85(m, 2H, AA'BB'), 7.07(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.30(m, 2H), 7.38(m, 2H), 7.54(m, 2H).
92		NMR(CDC13) $\delta$ 3.45(s, 3H), 3.77(s, 3H), 3.82(s, 3H), 5.41(s, 1H), 6.28(s, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.34(m, 2H), 7.47(m, 2H)
93		NMR(CDC13) $\delta$ 3.42(s, 3H), 3.46(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 4.47(s, 2H), 5.46(s, 1H), 6.29(s, 1H), 6.77(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.28(d, J=7.5Hz, 1H), 7.36(t, J=7.5Hz, 1H), 7.47(d, J=7.5Hz, 1H), 7.50(bs, 1H)
94		NMR(CDC13) $\delta$ 1.26(t, J=8.0Hz, 3H), 3.55-3.67(m, 2H), 3.78(s, 3H), 3.80(s, 3H), 5.53(s, 1H), 6.31(s, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.04(t, J=9.0Hz, 2H), 7.09(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.50(dd, J=9.0, 5.5Hz, 2H)
95		NMR(CDC13) $\delta$ 3.25(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 5.44(s, 1H), 6.30(s, 1H), 6.77(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.25-7.34(m, 2H), 7.37(d, J=8.0Hz, 1H), 7.54(d, J=8.0Hz, 1H)
96		NMR(CDC13) $\delta$ 3.47(s, 3H), 3.76(s, 3H), 3.80(s, 3H), 5.47(s, 1H), 6.25(s, 1H), 6.77(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.19(m, 2H, AA'BB'), 7.65(s, 4H)
97		NMR(CDC13) $\delta$ 3.46(s, 3H), 3.77(s, 3H), 3.81(s, 3H), 3.97(s, 3H), 5.45(s, 1H), 6.29(s, 1H), 6.77(m, 2H, AA'BB'), 6.83(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.38(t, J=8.0Hz, 1H), 7.53-7.57(m, 2H), 7.74(s, 1H), 8.08(s, 1H)

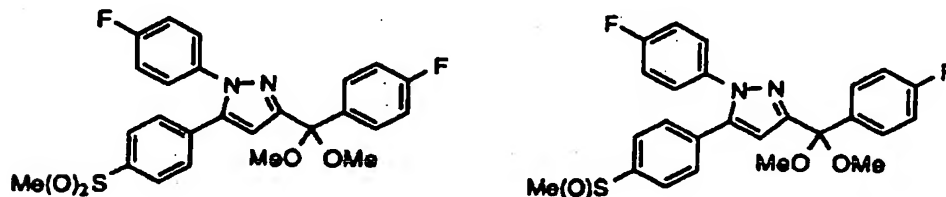
Table 17

Ex.no.	Chemical formula	NMR data
98		NMR(CDC13)δ 3.43(s, 3H), 3.77(s, 3H), 3.79(s, 3H), 4.06(s, 2H), 5.14(bs, 1H), 5.43(s, 1H), 6.32(s, 1H), 6.77(m, 2H, AA'BB'), 6.82(m, 2H, AA'BB'), 7.08(m, 2H, AA'BB'), 7.19(m, 2H, AA'BB'), 7.28(d, J=8.0Hz, 1H), 7.35(t, J=8.0Hz, 1H), 7.46(d, J=8.0Hz, 1H), 7.53(s, 1H)
99		NMR(CDC13)δ 3.47(s, 3H), 3.77(s, 3H), 3.80(s, 3H), 5.43(s, 1H), 6.26(s, 1H), 6.79(m, 2H, AA'BB'), 6.85(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.48(d, J=8.5Hz, 1H), 7.68(dd, J=8.5, 2.5Hz, 1H), 7.84(d, J=2.0Hz, 1H)
100		NMR(CDC13)δ 2.88(t, J=6.5Hz, 2H), 3.45(s, 3H), 3.78(s, 3H), 3.81(s, 3H), 3.87(q, J=6.5Hz, 2H), 5.42(s, 1H), 6.32(s, 1H), 6.78(m, 2H, AA'BB'), 6.84(m, 2H, AA'BB'), 7.10(m, 2H, AA'BB'), 7.20(m, 2H, AA'BB'), 7.24(d, J=8.0Hz, 2H), 7.49(d, J=8.0Hz, 2H)
101		NMR(CDC13)δ 3.47(s, 3H), 3.79(s, 3H), 3.81(s, 3H), 5.70(s, 1H), 6.49(s, 1H), 6.80(m, 2H, AA'BB'), 6.85(m, 2H, AA'BB'), 6.98(dd, J=5.0, 3.5Hz, 1H), 7.09(dt, J=3.5, 1.0Hz, 1H), 7.13 (m, 2H, AA'BB'), 7.22(m, 2H, AA'BB'), 7.31(dd, J=5.0, 1.0Hz, 1H)
102		NMR(CDC13)δ 2.99(s, 3H), 3.46(s, 3H), 3.78(s, 3H), 3.81(s, 3H), 1.94-2.12(m, 4H), 3.80- 3.92(m, 4H), 5.45(s, 1H), 6.29(s, 1H), 6.78(m, 2H, AA'BB'), 6.85(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'), 7.21(m, 2H, AA'BB'), 7.33(bd, J=7.5Hz, 1H), 7.38(t, J=7.5Hz, 1H), 7.45(bd, J=7.5Hz, 1H), 7.59(bs, 1H)

Example 103

1-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazol-  
3-yl 4-fluorophenyl ketone dimethyl acetal

1-(4-Fluorophenyl)-5-(4-methylsulfinylphenyl)pyrazol-3-yl 4-fluorophenyl ketone dimethyl acetal



1.5 g of a mixture of 1-(4-fluorophenyl)-5-(4-methylsulfinylphenyl)pyrazol-3-yl 4-fluorophenyl ketone and 1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazol-3-yl 4-fluorophenyl ketone was suspended in 70 ml of methanol. Then 11.8 g (111 mmol) of trimethyl orthoformate and 800 mg (4 mmol) of p-toluenesulfonic acid monohydrate were added to the suspension and the resulting mixture was heated under reflux for 12 hours. After cooling, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. Then, water was added to the neutralized reaction mixture, followed by the extraction with ethyl acetate. The organic phase was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. After filtering, the filtrate was distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography with the use of

60 g of silica gel. Thus, 700 mg of 1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazol-3-yl 4-fluorophenyl ketone dimethyl acetal was obtained from the fraction eluted with ethyl acetate/n-hexane (2 : 3), while 500 mg of 1-(4-fluorophenyl)-5-(4-methylsulfinylphenyl)pyrazol-3-yl 4-fluorophenyl ketone dimethyl acetal was obtained from a fraction eluted with ethyl acetate/n-hexane (9 : 1) each in the form of pale yellow crystals.

1-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazol-3-yl 4-fluorophenyl ketone dimethyl acetal

NMR(DMSO- $d_6$ ) $\delta$ :

3.14(s, 6H), 3.22(s, 3H), 6.84(s, 1H), 7.17(t, J=9.0Hz, 2H), 7.21-7.30(m, 4H), 7.47(m, 2H, AA'BB'), 7.55(m, 2H), 7.86(m, 2H, AA'BB')

1-(4-Fluorophenyl)-5-(4-methylsulfinylphenyl)pyrazol-3-yl 4-fluorophenyl ketone dimethyl acetal

NMR(DMSO- $d_6$ ) $\delta$ :

2.73(s, 3H), 3.14(s, 6H), 6.77(s, 1H), 7.18(t, J=8.9Hz, 2H), 7.20-7.27(m, 4H), 7.40(m, 2H, AA'BB'), 7.55(m, 2H), 7.63(m, 2H, AA'BB')

The compounds described in the following Tables 18 to 22 were prepared in the similar manner as that of Example 103.

Table 18

Ex.no.	Chemical formula	NMR data
104		NMR(CDCl <sub>3</sub> ) $\delta$ 3.28 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 6.35 (s, 1H), 7.21 (t, J=7.9Hz, 1H), 6.78 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.19 (m, 2H, AA'BB'), 7.41 (d, J=7.9Hz, 1H), 7.59 (d, J=7.9Hz, 1H), 7.86 (s, 1H)
105		NMR(CDCl <sub>3</sub> ) $\delta$ 3.28 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 6.35 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 6.97 (bt, J=9.0Hz, 1H), 7.09 (m, 2H, AA'BB'), 7.18 (m, 2H, AA'BB'), 7.30 (dt, J=9.0, 6.0Hz, 1H), 7.41 (bd, J=9.0Hz, 1H), 7.45 (bd, J=9.0Hz, 1H)
106		NMR(CDCl <sub>3</sub> ) $\delta$ 3.28 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 6.33 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.02 (t, J=9.0Hz, 2H), 7.09 (m, 2H, AA'BB'), 7.18 (m, 2H, AA'BB'), 7.65 (dd, J=9.0, 5.5Hz, 2H)
107		NMR(CDCl <sub>3</sub> ) $\delta$ 2.47 (s, 3H), 3.27 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 6.33 (s, 1H), 6.76 (m, 2H, AA'BB'), 6.80 (m, 2H, AA'BB'), 7.07 (d, J=9.0Hz, 2H), 7.18 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'), 7.69 (d, J=9.0Hz, 2H)
108		NMR(CDCl <sub>3</sub> ) $\delta$ 3.27 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 6.32 (s, 1H), 6.76 (m, 2H, AA'BB'), 6.80 (m, 2H, AA'BB'), 6.87 (d, J=8.0Hz, 2H), 7.08 (m, 2H, AA'BB'), 7.19 (m, 2H, AA'BB'), 7.59 (d, J=8.0Hz, 2H)
109		NMR(CDCl <sub>3</sub> ) $\delta$ 3.38 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 6.36 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.17 (m, 2H, AA'BB'), 7.60 (d, J=8.0Hz, 2H), 7.80 (d, J=8.0Hz, 2H)
110		NMR(CDCl <sub>3</sub> ) $\delta$ 3.28 (s, 6H), 3.80 (s, 3H), 6.39 (s, 1H), 6.81 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.16 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'), 7.29 (m, 1H), 7.35 (m, 2H), 7.68 (m, 2H)

Table 19

111		NMR(CDC13)δ 3.28 (s, 6H), 3.78 (s, 3H), 6.40 (s, 1H), 6.80 (m, 2H, AA'BB'), 7.14-7.17 (m, 2H), 7.18 (m, 2H, AA'BB'), 7.22-7.31 (m, 4H), 7.36 (m, 2H), 7.69 (m, 2H).
112		NMR(CDC13)δ 3.38 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 6.36 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.17 (m, 2H, AA'BB'), 7.46 (t, J=8.0Hz, 1H), 7.54 (d, J=8.0Hz, 1H), 7.84 (d, J=8.0Hz, 1H) 8.00 (s, 1H)
113		NMR(CDC13)δ 2.45 (s, 3H), 3.28 (s, 6H), 3.80 (s, 3H), 6.39 (s, 1H), 6.81 (m, 2H, AA'BB'), 6.97 (dt, J=2.5, 9.0Hz, 1H), 7.07 (m, 2H, AA'BB'), 7.10 (m, 2H, AA'BB'), 7.18 (m, 2H, AA'BB'), 7.31 (dd, J=8.0, 5.5Hz, 1H), 7.40 (dt, J=8.0, 2.5Hz, 1H), 7.44 (dt, J=9.0, 2.5Hz, 1H)
114		NMR(CDC13)δ 3.78 (s, 3H), 3.79 (s, 3H), 4.07 (m, 2H), 4.25 (m, 2H), 6.36 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.05 (t, J=9.0Hz, 2H), 7.09 (m, 2H, AA'BB'), 7.19 (m, 2H, AA'BB'), 7.68 (dd, J=9.0, 5.5Hz, 2H)
115		NMR(CDC13)δ 3.27 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 6.34 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.18 (m, 2H, AA'BB'), 7.32 (m, 2H), 7.62 (m, 2H)
116		NMR(CDC13)δ 3.77 (s, 3H), 3.79 (s, 3H), 4.05 (m, 2H), 4.25 (m, 2H), 6.36 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.80 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.18 (m, 2H, AA'BB'), 7.34 (d, J=8.8Hz, 2H), 7.65 (d, J=8.8Hz, 2H)
117		NMR(DMSO-d6)δ 3.13 (s, 6H), 3.71 (s, 3H), 3.73 (s, 3H), 6.50 (s, 1H), 6.73 (s, 2H), 6.85 (m, 2H, AA'BB'), 6.91 (m, 2H, AA'BB'), 7.10 (m, 4H), 8.47 (s, 1H)

Table 20

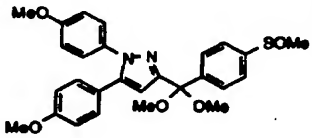
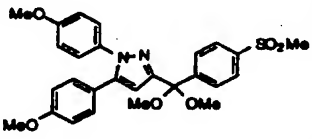
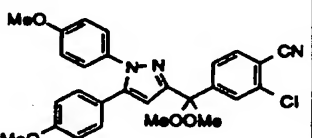
EX.no.	Chemical formula	NMR data
118		NMR (CDCl <sub>3</sub> ) δ 3.29 (s, 6H), 3.78 (s, 6H), 6.55 (s, 1H), 6.79 (m, 2H, AA'BB'), 6.79 (m, 2H, AA'BB'), 7.12 (m, 2H, AA'BB'), 7.15 (m, 2H, AA'BB'), 7.06-7.18 (m, 2H), 7.67-7.72 (m, 1H)
119		NMR (CDCl <sub>3</sub> ) δ 1.41 (s, 6H), 2.55 (s, 3H), 3.28 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 4.17 (s, 2H), 6.33 (s, 1H), 6.76 (m, 2H, AA'BB'), 6.81 (d, 2H, J=6.8Hz), 7.08 (m, 2H, AA'BB'), 7.19 (d, 2H, J=6.8Hz), 7.21 (m, 2H, AA'BB'), 7.59 (m, 2H, AA'BB'), 8.06 (s, 1H)
120		NMR (CDCl <sub>3</sub> ) δ 1.44 (s, 6H), 3.27 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 4.15 (s, 2H), 6.36 (s, 1H), 6.78 (d, 2H, J=8.4Hz), 6.81 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.17 (m, 2H, AA'BB'), 7.41 (m, 2H, AA'BB'), 7.65 (dd, 1H, J=8.4, 2.0Hz), 8.05 (d, 1H, J=2.0Hz)
121		NMR (CDCl <sub>3</sub> ) δ 3.11 (s, 6H), 3.72 (s, 3H), 3.74 (s, 3H), 6.53 (s, 1H), 6.86 (m, 2H, AA'BB'), 6.90 (m, 2H, AA'BB'), 6.91 (d, J=8.5Hz, 1H), 7.09 (m, 2H, AA'BB'), 7.12 (m, 2H, AA'BB'), 7.22 (dd, J=8.5, 2.5Hz, 1H), 7.40 (d, J=2.5Hz, 1H)
122		NMR (CDCl <sub>3</sub> ) δ 3.34 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 6.40 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.82 (m, 2H, AA'BB'), 6.99 (dd, J=5.0, 3.5Hz, 1H), 7.11 (m, 2H, AA'BB'), 7.15 (dd, J=3.5, 1.5Hz, 1H), 7.21 (m, 2H, AA'BB'), 7.28 (dd, J=5.0, 1.0Hz, 1H)
123		NMR (DMSO-d <sub>6</sub> ) δ 3.15 (s, 6H), 3.71 (s, 3H), 3.73 (s, 3H), 5.46 (s, 2H), 6.52 (s, 1H), 6.86 (m, 2H, AA'BB'), 6.90 (m, 2H, AA'BB'), 6.98 (dd, J=8.5, 2.5Hz, 1H), 7.09 (m, 2H, AA'BB'), 7.11 (m, 2H, AA'BB'), 7.16 (s, 1H), 7.16 (d, J=8.5Hz, 1H), 7.30 (t, J=8.5Hz, 1H)
124		NMR (DMSO-d <sub>6</sub> ) δ 3.13 (s, 6H), 3.71 (s, 3H), 3.73 (s, 3H), 5.46 (s, 2H), 6.52 (s, 1H), 6.86 (m, 2H, AA'BB'), 6.90 (m, 2H, AA'BB'), 6.98 (dd, J=8.5, 2.5Hz, 1H), 7.09 (m, 2H, AA'BB'), 7.11 (m, 2H, AA'BB'), 7.16 (s, 1H), 7.16 (d, J=8.5Hz, 1H), 7.30 (t, J=8.5Hz, 1H)



Table 21

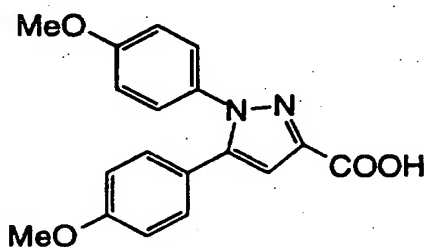
Ex.no.	Chemical formula	NMR data
125		NMR(CDCl <sub>3</sub> ) $\delta$ 2.78 (s, 3H), 3.30 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 6.37 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.19 (m, 2H, AA'BB'), 7.43 (d, 1H, J=8.4Hz), 7.56 (dd, 1H, J=8.4, 2.4Hz), 7.56 (s, 1H), 8.19 (d, 1H, J=2.4Hz)
126		NMR(CDCl <sub>3</sub> ) $\delta$ 3.24 (s, 6H), 3.78 (s, 3H), 3.79 (s, 3H), 6.35 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.80 (m, 2H, AA'BB'), 7.00 (d, 1H, J=15.2Hz), 7.07 (m, 2H, AA'BB'), 7.13 (m, 2H, AA'BB'), 7.40 (d, 1H, J=8.4Hz), 7.54-7.66 (m, 4H), 7.89 (d, 1H, J=2.4Hz), 7.95-7.99 (m, 2H), 8.09 (d, 1H, J=15.2Hz)
127		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.17 (s, 6H), 3.71 (s, 3H), 3.72 (s, 3H), 6.60 (s, 1H), 6.86 (m, 2H, AA'BB'), 6.89 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.12 (m, 2H, AA'BB'), 7.47 (dd, 1H, J=8.4, 2.4Hz), 7.54 (d, 1H, J=8.4Hz), 8.14 (s, 1H) 8.36 (s, 1H)
128		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.15 (s, 6H), 3.71 (s, 3H), 3.73 (s, 3H), 6.60 (s, 1H), 6.86 (m, 2H, AA'BB'), 6.90 (m, 2H, AA'BB'), 7.07 (m, 2H, AA'BB'), 7.11 (m, 2H, AA'BB'), 7.69 (d, J=8.0Hz, 2H), 7.82 (d, J=8.0Hz, 2H)
129		NMR(CDCl <sub>3</sub> ) $\delta$ 3.01 (s, 3H), 3.26 (s, 6H), 3.79 (s, 3H), 6.39 (bs, 1H), 6.42 (s, 1H), 6.81 (m, 2H, AA'BB'), 7.16 (m, 2H, AA'BB'), 7.18 (m, 2H, AA'BB'), 7.23-7.27 (m, 5H) 7.66 (m, 2H, AA'BB')
130		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.22 (s, 3H), 3.97 (m, 2H), 4.12 (m, 2H), 6.81 (s, 1H), 7.17 (t, J=8.8Hz, 2H), 7.22- 7.31 (m, 4H), 7.47 (m, 2H, AA'BB'), 7.57 (m, 2H), 7.86 (m, 2H, AA'BB')
131		NMR(DMSO-d <sub>6</sub> ) $\delta$ 2.73 (s, 3H), 3.97 (m, 2H), 4.12 (m, 2H), 6.74 (s, 1H), 7.17 (m, 2H), 7.21-7.29 (m, 4H), 7.40 (m, 2H, AA'BB'), 7.57 (m, 2H), 7.63 (m, 2H, AA'BB')

Table 22

Ex.no.	Chemical formula	NMR data
132		NMR(CDCl <sub>3</sub> ) $\delta$ 2.73 (s, 3H), 3.28 (s, 6H), 3.78 (s, 3H), 3.79 (s, 3H), 6.38 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.17 (m, 2H, AA'BB'), 7.63 (d, J=9.0Hz, 2H), 7.85 (d, J=9.0Hz, 2H)
133		NMR(CDCl <sub>3</sub> ) $\delta$ 3.96 (s, 3H), 3.28 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 6.39 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.16 (m, 2H, AA'BB'), 7.90 (m, 4H)
134		NMR(DMSO-d <sub>6</sub> ) $\delta$ 3.16 (s, 6H), 3.72 (s, 3H), 3.73 (s, 3H), 6.65 (s, 1H), 6.86 (m, 2H, AA'BB'), 6.90 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.12 (m, 2H, AA'BB'), 7.61 (dd, J=8.0, 1.5Hz, 1H), 7.78 (d, J=1.5Hz, 1H), 7.96 (d, J=8.0Hz, 1H)

Example 1351,5-Bis(4-methoxyphenyl)pyrazol-3-yl-3-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)]-4-chlorophenyl ketone

(1) Synthesis of 1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxylic acid

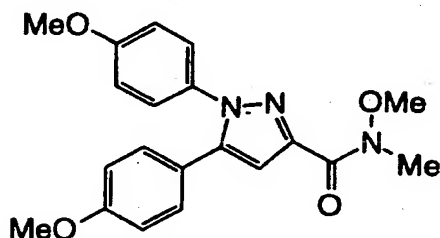


370 g (1.05 mol) of ethyl 1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxylate was dispersed in 4 liters of ethanol. Thereto was added 500 ml of 5N NaOH solution and the mixture was stirred at room temperature for 1 hour. 4 liters of water and 3 liters of saturated aqueous solution of sodium chloride were added thereto and the mixture was extracted with 4 liters of ethyl acetate. It was washed with 3 liters of saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. Distillation of the solvent under a reduced pressure produced crystals, which were washed twice with IPE and then dried with blown air for 13 hours within a drying chamber at room temperature. 292.4 g (0.90 mol) of 1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxylic acid, white crystals, was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ :

3.76 (s, 3H), 3.78 (s, 3H), 6.78 (m, 2H, AA'BB'),  
6.83 (m, 2H, AA'BB'), 6.93 (s, 1H), 7.10 (m, 2H, AA'BB'),  
7.22 (m, 2H, AA'BB')

(2) Synthesis of *N*-methoxy-*N*-methyl-1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxamide



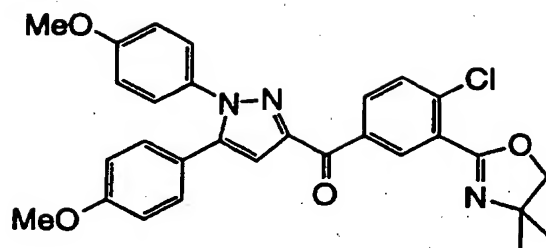
To 290 g (0.89 mol) of 1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxylic acid obtained in the step (1) was added 300 ml of thionyl chloride. The mixture was heated under reflux for 1.5 hours. The excess of thionyl chloride was distilled out under a reduced pressure. The product mixture was boiled azeotropically with toluene three times to remove the thionyl chloride completely. The obtained brown oil was dissolved in 1.5 liters of tetrahydrofuran and cooled with ice bath. Thereto was added 130g (1.34 mol) of *N*,*O*-dimethylhydroxylamine hydrochloric acid salt and followed by dropwise addition of 372

ml (2.67 mol) of triethylamine. The mixture was stirred for 2 hours, cooled with ice bath. Thereto was added ethyl acetate. It was washed in the order with 1N aqueous solution of hydrochloric acid, saturated aqueous solution of sodium bicarbonate and saturated aqueous solution of sodium chloride. It was dried with anhydrous magnesium sulfate. The solvent was distilled out under reduced pressure to obtain the residue, to which was added 500 ml of diethyl ether. The mixture was allowed to stand over night to obtain 218.5 g of crude crystals of *N*-methoxy-*N*-methyl-1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxamide. It was used for the subsequent step, no further purification effected.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ:

3.82(s, 3H), 3.84(s, 3H), 3.97(s, 3H), 6.85(m, 2H, AA'BB'),  
6.89(m, 2H, AA'BB'), 7.12(s, 1H), 7.18(m, 2H, AA'BB'),  
7.28(m, 2H, AA'BB'), 7.56(d, 1H, J=8.5Hz),  
8.50(dd, 1H, J=8.5, 2.0Hz), 8.90(d, 1H, J=2.0Hz)

(3) Synthesis of 1,5-bis(4-methoxyphenyl)pyrazol-3-yl-3-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)]-4-chlorophenyl ketone



218.5 g (0.59 mol) of *N*-methoxy-*N*-methyl-1,5-bis(4-methoxyphenyl)-3-pyrazolecarboxamide and 206 g (0.71 mol) of 2-(5-bromo-2-chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole were dissolved in 2.2 liters of anhydrous tetrahydrofuran. To the solution was added dropwise 444 ml (0.71 mol) of *n*-butyl lithium in 1.6N solution of *n*-hexane at temperature of minus 70 °C or below over the period of 1 hour.

It was stirred at minus 70 °C for 2 hours, to which was added 2 liters of water. It was extracted with 4 liters of ethyl acetate. The extracts were washed with 3 liters of saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was distilled out under reduced pressure to obtain the residue, to which was added diethyl ether. It was allowed to stand at 4°C over one night for crystallization. The crystals were filtered and washed with a cooled diethyl ether, then dried under a reduced pressure to obtain 120 g of light pink-gray powder. The residue was collected by distilling out the solvent under reduced pressure. It was treated with column

chromatography using 4 kg of silicagel to obtain 158 g (52%) 1,5-bis(4-methoxyphenyl)pyrazol-3-yl-3-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)]-4-chlorophenyl ketone.

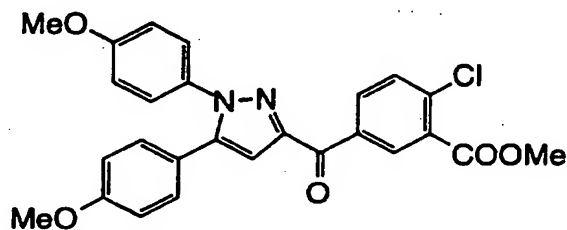
$^1\text{H-NMR}(\text{CDCl}_3)\delta$ :

1.50(s, 6H), 3.82(s, 3H), 3.83(s, 3H), 4.25(s, 2H),  
6.86(m, 2H, AA'BB'), 6.88(m, 2H, AA'BB'), 7.12(s, 1H),  
7.18(m, 2H, AA'BB'), 7.31(m, 2H, AA'BB'), 7.57(d, 1H, J=8.4Hz),  
8.49(dd, 1H, J=8.4, 2.2Hz), 8.89(d, 1H, J=2.2Hz)

m.p.: 161-163°C

#### Example 136

Methyl 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoate



To 145.2 g (0.31 mol) of 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoic acid as obtained in Example 2 and 300 ml of solution of 85 g (0.6 mol) of methyl iodide in N,N-dimethylformamide was added, cooled with ice bath, 0.62 mol of sodium hydride which had been washed with

n-hexane. The mixture was stirred at room temperature for 1 hour and then poured into iced water. The precipitates were collected by filtration and washed with water, then dissolved in dichloromethane and ethyl acetate. The organic phase was washed with water and dried with anhydrous magnesium sulfate. The solvent was distilled out under reduced pressure to obtain 142 g (0.30 mol, 97%) of yellow clay-colored solid, methyl 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoate.

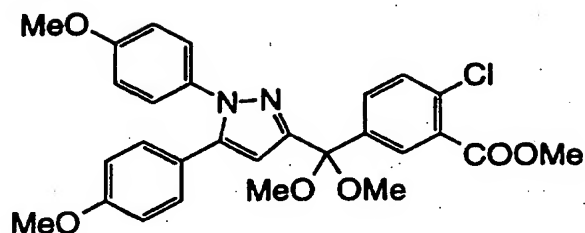
<sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ:

3.82(s, 3H), 3.84(s, 3H), 3.97(s, 3H), 6.85(m, 2H, AA'BB'),  
6.89(m, 2H, AA'BB'), 7.12(s, 1H), 7.18(m, 2H, AA'BB'),  
7.28(m, 2H, AA'BB'), 7.56(d, 1H, J=8.5Hz),  
8.50(dd, 1H, J=8.5, 2.0Hz), 8.90(d, 1H, J=2.0Hz)

#### Example 137

Methyl 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-chlorobenzoate





To 1 liter of solution in methanol of 143 g (0.3 mol) of methyl 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoate obtained in Example 136, were added 955 g (9 mol) of trimethyl orthoformate and 11.4 g (0.06 mol) of p-toluenesulfonic acid monohydrate. The mixture was heated under reflux over night. In order to complete the reaction, additional 200 ml of trimethyl orthoformate, 200 ml of methanol and 5.7 g of p-toluenesulfonic acid monohydrate were added thereto and the mixture was heated under reflux for 6 hours. Then 500 ml of trimethyl orthoformate, 500 ml of methanol and 5.7 g of p-toluenesulfonic acid monohydrate were added thereto and the mixture was heated under reflux over night. Part of the raw materials still remained. Having stopped heating with reflux, having cooled it, saturated aqueous solution of sodium bicarbonate and saturated aqueous solution of sodium chloride were added thereto. It was extracted twice with ethyl acetate. The extract was washed three times with saturated aqueous solution of sodium chloride and dried with anhydrous magnesium

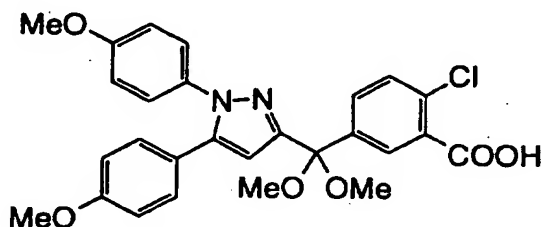
sulfate. The solvent was distilled out under reduced pressure to obtain the residue, which was then treated with column chromatography using 4 kg of silicagel to obtain 74.3g of methyl 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-chlorobenzoate as light yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ :

3.28 (s, 6H), 3.78 (s, 3H), 3.79 (s, 3H), 3.93 (s, 3H), 6.37 (1H, s),  
6.77-6.82 (m, 4H), 7.08-7.18 (m, 4H), 7.43 (d, 1H,  $J=8.4\text{Hz}$ ),  
7.71 (dd, 1H,  $J=8.4, 2.4\text{Hz}$ ), 8.15 (d, 1H,  $J=2.4\text{Hz}$ )

Example 138

5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-  
dimethoxymethyl]-2-chlorobenzoic acid



To 400 ml of solution in ethanol of 74.3 g (147 mmol) of methyl 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-chlorobenzoate obtained in Example 137 was

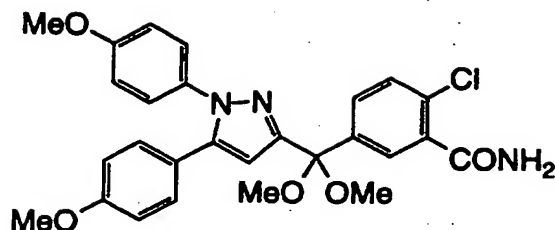
added 120 ml of 5N aqueous solution of sodium hydroxide. The mixture was heated at 50 °C, being stirred for 1 hour. The reaction mixture was cooled with ice bath and rendered acidic at about pH 3 with 1N aqueous solution of hydrochloric acid and immediately extracted twice with ethyl acetate. It was washed twice with saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was distilled out under reduced pressure to obtain 72.47 g (97%) of 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-chlorobenzoic acid, as light yellow oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ:

3.27(s, 6H), 3.75(s, 3H), 3.77(s, 3H), 6.51(s, 1H),  
6.76(m, 2H, AA'BB'), 6.79(m, 2H, AA'BB'), 7.09(m, 2H, AA'BB'),  
7.21(m, 2H, AA'BB'), 7.40(d, 1H, J=8.5Hz),  
7.61(dd, 1H, J=8.5, 2.0Hz), 8.38(d, 1H, J=2.0Hz)

#### Example 139

5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-  
dimethoxymethyl]-2-chlorobenzamide

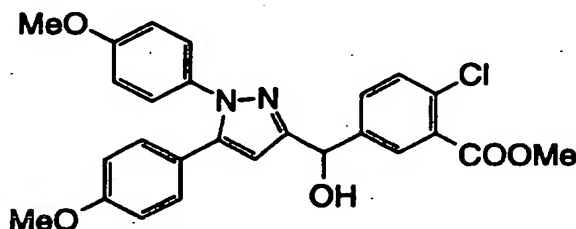


To 350 ml of solution in N,N-dimethylformamide of 72.47 g (147 mmol) of 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-chlorobenzoic acid was added 40 g (294 mmol) of 1-hydroxybenzotriazol (HOBt). To the obtained dispersion was added, cooled with ice bath, 45.6 g (294 mmol) of water-soluble carbodiimide (WSCD). The mixture was stirred at room temperature over night to obtain transparent solution. Ammonia gas was blown thereinto at room temperature to obtain crystals. It was stirred at room temperature for 1.5 hours and then saturated aqueous solution of sodium bicarbonate and water were added thereto. It was extracted twice with ethyl acetate, washed three times with water, once with saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was distilled out under reduced pressure to obtain the residue, which was treated with column chromatography using 2 kg of silicagel NAM200H. Having been purified eluting with methanol-dichloromethane: 0.5-2% solution, 64 g of 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-

yl]-1,1-dimethoxymethyl]-2-chlorobenzamide, white solid, was obtained.

Example 140

Methyl ( $\pm$ )-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-hydroxymethyl]-2-chlorobenzoate



2.0 g (4.3 mmol) of ( $\pm$ )-5-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]hydroxymethyl-2-chlorobenzoic acid, obtainable by the process shown in Example 39, was dissolved in solvent mixture of methanol and dichloromethane. Thereto was added at room temperature 10 ml of 10% solution in dichloromethane of trimethylsilyldiazomethane. The mixture was stirred at the same temperature as before for 2 hours. The solvent was distilled out to obtain the residue, which was then purified by silicagel column chromatography eluting with ethyl acetate-n-hexane at 30%-40% to obtain 1.13 g of methyl ( $\pm$ )-

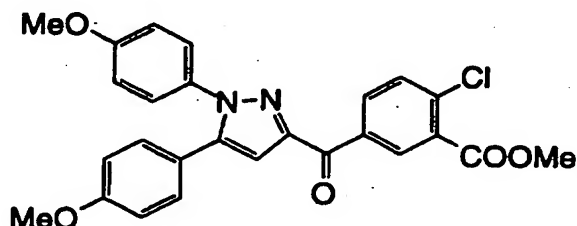
5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-hydroxymethyl]-2-chlorobenzoate as colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ :

3.68 (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H), 5.88 (s, 1H), 6.08 (s, 1H),  
6.70 (m, 2H, AA'BB'), 6.78 (m, 2H, AA'BB'), 7.00 (m, 2H, AA'BB'),  
7.12 (m, 2H, AA'BB'), 7.18 (s, 1H), 7.38 (d, 1H,  $J=8.5\text{Hz}$ ),  
7.52 (dd, 1H,  $J=8.5, 2.0\text{Hz}$ ), 7.94 (d, 1H,  $J=2.0\text{Hz}$ )

Example 141

Methyl 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoate

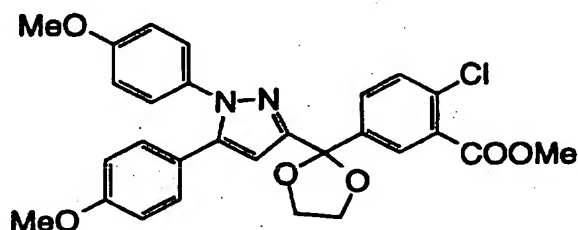


1.13 g (2.4 mmol) of methyl ( $\pm$ )-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-hydroxymethyl]-2-chlorobenzoate obtained in Example 140 was dissolved in 60 ml of 1,2-dichloroethane. Thereto was added 5 g of manganese dioxide. The mixture was heated under reflux for 3 hours. It was cooled and the insoluble was filtered out. The solvent was

distilled out under reduced pressure from the liquid to obtain 1.06 g of methyl 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-chlorobenzoate as colorless solid.

Example 142

Methyl 5-[2-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzoate



To 20 ml of solution in toluene of 0.42 g (0.8 mmol) of methyl 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-chlorobenzoate obtained in Example 137 were added 20 mg of p-toluenesulfonic acid monohydrate and 100 mg of ethylene glycol. The mixture was heated under reflux for 2 hours with azeotropic removal of water. It was cooled and saturated aqueous solution of sodium bicarbonate was added thereto. The mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was

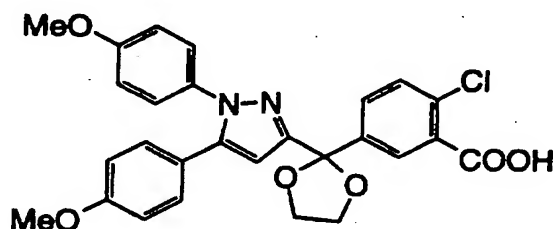
distilled out under reduced pressure to obtain the residue, which was purified with silicagel column chromatography eluting with ethyl acetate-n-hexane at 20-30% to obtain 0.28 g of methyl 5-[2-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzoate, as colorless solid.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ :

3.78 (s, 3H), 3.79 (s, 3H), 3.92 (s, 3H), 4.05 (m, 2H), 4.26 (m, 2H),  
6.38 (s, 1H), 6.80 (m, 4H), 7.08 (m, 2H), 7.17 (m, 2H),  
7.45 (d, 1H,  $J=8.5\text{Hz}$ ), 7.76 (dd, 1H,  $J=8.5, 2.0\text{Hz}$ ),  
8.17 (d, 1H,  $J=2.0\text{Hz}$ ).

Example 143

5-[2-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzoic acid



To dispersion of 0.28 g of methyl 5-[2-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzoate obtained in Example 142 in 50ml of solvent mixture



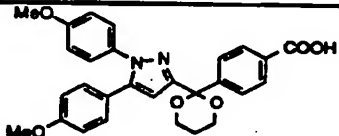
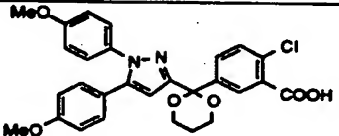
of methanol and water (2:1), was added 1 ml of 5N aqueous solution of sodium hydroxide. The mixture was heated and stirred for 1.5 hours at 40 °C. The suspension turned to solution. It was neutralized with 1N hydrochloric acid, mixed with saturated aqueous solution of sodium chloride and extracted with ethyl acetate. The organic phase was washed with saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was distilled out under reduced pressure to obtain 0.28 g of 5-[2-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzoic acid as colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>+DMSO-d<sub>6</sub>) δ:

3.70 (s, 6H), 3.90 (m, 2H), 4.10 (m, 2H), 6.33 (s, 1H), 6.71 (m, 4H),  
7.01 (m, 2H), 7.09 (m, 2H), 7.18-7.25 (m, 1H), 7.48 (m, 1H),  
8.01 (m, 1H).

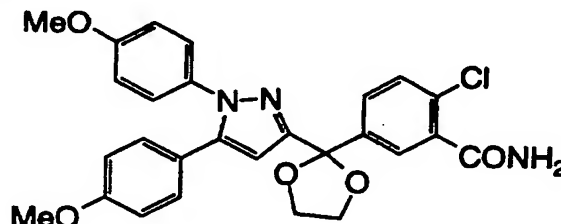
The compounds shown in Table 23 were obtained in the same manner as that of Example 143.

Table 23

Ex.no.	Chemical formula	NMR data
144		NMR (CDCl <sub>3</sub> ) δ 1.85 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.06 (m, 2H), 4.25 (m, 2H), 6.40 (s, 1H), 6.76 (m, 2H), 6.79 (m, 2H), 7.07 (m, 2H), 7.17 (m, 2H), 7.80 (m, 2H), 8.11 (m, 2H)
145		NMR (CDCl <sub>3</sub> ) δ 1.66-1.90 (m, 2H), 3.73 (s, 6H), 3.99 (m, 2H), 4.16 (m, 2H), 6.36 (s, 1H), 6.74 (m, 4H), 7.04 (m, 2H), 7.13 (m, 2H), 7.35 (m, 1H), 7.61 (m, 1H), 8.13 (m, 1H)

Example 146

5-[2-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzamide



To 20 ml of N,N-dimethylformamide solution of 0.26 g of 5-[2-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzoic acid obtained in Example 143, was added at room temperature 0.26 g of 1-hydroxybenzotriazol (HOBt). To the obtained reaction mixture was added, at same temperature, 0.26 g of water-soluble carbodiimide (WSCD). The mixture was stirred

at room temperature over 2 hours. Ammonia gas was blown thereinto at room temperature for 30 minutes. It was stirred at room temperature over night. Saturated aqueous solution of sodium bicarbonate was added. It was extracted with ethyl acetate and washed twice with saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was distilled out under reduced pressure to obtain the residue, which was purified with column chromatography using silicagel to obtain 0.12 g of 5-[2-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,3-dioxolan-2-yl]-2-chlorobenzamide, as colorless foamed product.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:

3.78 (s, 3H), 3.79 (s, 3H), 4.05 (m, 2H), 4.25 (m, 2H),  
5.82 (bs, 1H), 6.34 (bs, 1H), 6.42 (s, 1H), 6.78 (m, 2H, AA'BB'),  
6.80 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.16 (m, 2H, AA'BB'),  
7.42 (d, J=8.5Hz, 1H), 7.73 (dd, J=8.5, 2.5Hz, 1H),  
8.06 (d, J=2.5Hz, 1H).

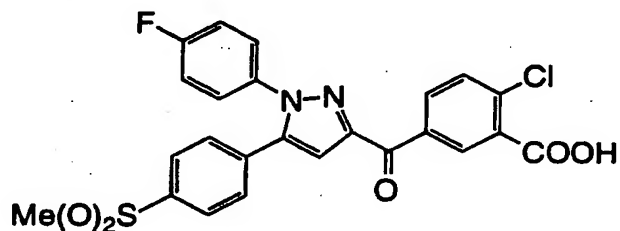
The compounds shown in Table 24 were obtained in the same manner as that of Example 146.

Table 24

Ex.no.	Chemical formula	NMR data
147		NMR(CDCl <sub>3</sub> ) $\delta$ 3.77 (s, 3H), 3.78 (s, 3H), 4.05 (m, 2H), 4.27 (m, 2H), 5.71 (bs, 1H), 6.15 (bs, 1H), 6.38 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.80 (m, 2H, AA'BB'), 7.08 (m, 2H, AA'BB'), 7.17 (m, 2H, AA'BB'), 7.78 (m, 2H, AA'BB'), 7.81 (m, 2H, AA'BB')
148		NMR(CDCl <sub>3</sub> ) $\delta$ 1.86 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.07 (m, 2H), 4.26 (m, 2H), 5.62 (bs, 1H), 6.11 (bs, 1H), 6.40 (s, 1H), 6.77 (m, 2H, AA'BB'), 6.80 (m, 2H, AA'BB'), 7.07 (m, 2H, AA'BB'), 7.16 (m, 2H, AA'BB'), 7.79 (m, 2H, AA'BB'), 7.82 (m, 2H, AA'BB')
149		NMR(CDCl <sub>3</sub> ) $\delta$ 1.77-1.93 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.06 (m, 2H), 4.25 (m, 2H), 5.92 (bs, 1H), 6.35 (bs, 1H), 6.43 (s, 1H), 6.78 (m, 2H, AA'BB'), 6.81 (m, 2H, AA'BB'), 7.09 (m, 2H, AA'BB'), 7.17 (m, 2H, AA'BB'), 7.42 (dJ=8.5Hz, 1H), 7.72 (dd, J=8.5, 2.5Hz, 1H), 8.03 (d, J=2.5Hz, 1H)

Example 150

2-Chloro-5-[1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazol-3-ylcarbonyl]benzoic acid



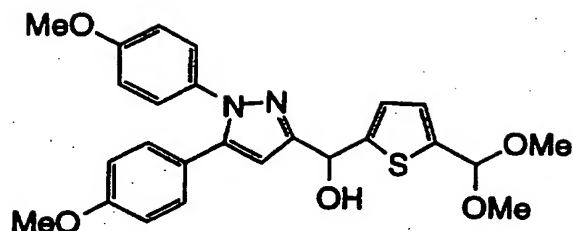
4.6 g (9.85 mmol) of 2-chloro-5-[1-(4-fluorophenyl)-5-(4-methylthiophenyl)pyrazol-3-ylcarbonyl]benzoic acid was dissolved in 250 ml of methanol and 50 ml of tetrahydrofuran. Thereto was added dropwise at room temperature 100 ml of aqueous solution of 18.2 g (29.6 mmol) of OXONE ( $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ ). The obtained whitened reaction mixture was stirred for 26 hours at room temperature. Water was added thereto. It was extracted with ethyl acetate, washed twice with water and once with saturated aqueous solution of sodium chloride and dried with anhydrous magnesium sulfate. The solvent was distilled out to obtain 4.6 g of 2-chloro-5-[1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazol-3-ylcarbonyl]benzoic acid as colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ :

3.25 (s, 3H), 7.35 (t,  $J=8.6\text{Hz}$ , 2H), 7.47 (s, 1H), 7.49-7.53 (m, 2H), 7.57 (m, 2H, AA'BB'), 7.76 (d,  $J=8.2\text{Hz}$ , 1H), 7.93 (m, 2H, AA'BB'), 8.43 (dd,  $J=8.2, 2.0\text{Hz}$ , 1H), 8.62 (d,  $J=2.0\text{Hz}$ , 1H)

#### Example 151

( $\pm$ )- $\alpha$ -(5-Dimethoxymethylthiophen-2-yl)-1,5-bis(4-methoxyphenyl)-3-pyrazolemethanol



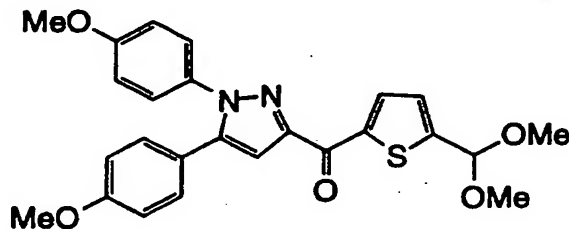
1.5 g (9.48 mmol) of 2-dimethoxymethylthiophene and 1.6 ml of N,N,N',N'-tetraethylenediamine were dissolved in 50 ml of anhydrous tetrahydrofuran. It was stirred under nitrogen gas at minus 78 °C. Thereto was added 6.5 ml (10.4 mmol) of 1.6 M solution of n-butyllithium in n-hexane. The reaction mixture was stirred for 2 hours. Thereto was added dropwise solution in 20 ml of anhydrous tetrahydrofuran of 2.7 g (8.76 mmol) of 1,5-bis(4-methoxyphenyl)-3-pyrazolecarbaldehyde. The reaction mixture was stirred at room temperature over night, to which was added water. It was extracted with ethyl acetate. The organic phase was washed with saturated aqueous solution of sodium chloride and dried with magnesium sulfate. Filtered solvent was distilled out to obtain the residue, which was purified with silicagel column chromatography eluting with n-hexane-ethyl acetate to obtain 2.17 g of light yellow, amorphous powder, (±)-α-(5-Dimethoxymethylthiophen-2-yl)-1,5-bis(4-methoxyphenyl)-3-pyrazolemethanol.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ:

3.08 (d, J=4.5Hz, 1H), 3.36 (s, 3H), 3.37 (s, 3H), 3.79 (s, 3H),  
3.81 (s, 3H), 5.59 (s, 1H), 6.14 (d, J=4.5Hz, 1H), 6.40 (s, 1H),  
6.79 (m, 2H, AA'BB'), 6.84 (m, 2H, AA'BB'),  
6.94 (bd, J=4.0Hz, 1H), 7.01 (bd, J=4.0Hz, 1H),  
7.11 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB')

Example 152

1,5-Bis(4-methoxyphenyl)pyrazol-3-yl 5-  
dimethoxymethylthiophen-2-yl ketone



1.9 g (4.1 mmol) of (±)-α-(5-dimethoxymethylthiophen-2-yl)-1,5-bis(4-methoxyphenyl)-3-pyrazolemethanol was dissolved in 200 ml of dichloromethane. The solution was stirred at room temperature. Thereto was added 20 g of manganese dioxide and the mixture was stirred at room temperature for 30 minutes. It was filtered through celite and the solvent was

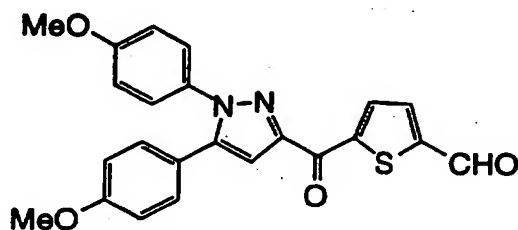
distilled out to obtain 1.90 g of light yellow crystals,  
1,5-bis(4-methoxyphenyl)pyrazol-3-yl 5-  
dimethoxymethylthiophen-2-yl ketone.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ :

3.38 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 5.67 (bs, 1H),  
6.85 (m, 2H, AA'BB'), 6.90 (m, 2H, AA'BB'), 7.10 (s, 1H),  
7.13 (dd,  $J=4.0, 0.5\text{Hz}$ , 1H), 7.17 (m, 2H, AA'BB'),  
7.30 (m, 2H, AA'BB'), 8.43 (d,  $J=4.0\text{Hz}$ , 1H)

Example 153

5-[1,5-Bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-  
thiophenecarbaldehyde



1.9 g (4.1 mmol) of 1,5-bis(4-methoxyphenyl)pyrazol-3-yl 5-dimethoxymethylthiophen-2-yl ketone was dispersed in solvent mixture of 90 ml of acetone and 10 ml of water. Thereto was added 0.76 g (4.1 mmol) of p-toluenesulfonic acid monohydrate.



The mixture was stirred at room temperature for 2 hours. Thereto was added saturated aqueous solution of sodium bicarbonate to neutralize it. It was extracted with ethyl acetate. The organic phase was washed with saturated solution of sodium chloride and dried with magnesium sulfate. The solvent was distilled out to obtain 1.59 g of 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-thiophenecarbaldehyde.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$ :

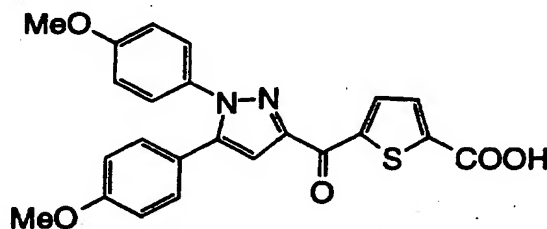
3.82 (s, 3H), 3.85 (s, 3H), 6.86 (m, 2H, AA'BB'),

6.92 (m, 2H, AA'BB'), 7.13 (s, 1H), 7.17 (m, 2H, AA'BB'),

7.30 (m, 2H, AA'BB'), 7.79 (d, J=4.0Hz, 1H), 8.48 (d, J=4.0Hz, 1H)

#### Example 154

5-[1,5-Bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-  
thiophenecarboxylic acid



0.5 g (1.2mmol) of 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-thiophenecarbaldehyde was dissolved in 20 ml of

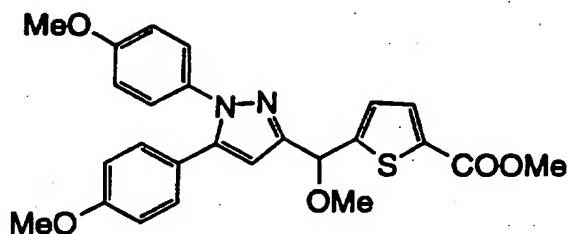
acetonitrile and 10 ml of dichloromethane. Thereto was added, cooled with ice bath bath, 62 mg of sodium dihydrogenphosphate, 0.5 ml of water and 0.15 ml of 30% aqueous hydrogen peroxide. Thereto was added solution in 9 ml of water of 0.13 g (1.4 mmol) of sodium chlorite. It was stirred at room temperature for 18 hours. Thereto was added 32 g of sodium sulfite and then diluted hydrochloric acid to render acidic the solution. The precipitates were collected and washed with water, then dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated solution of sodium chloride and dried with magnesium sulfate. The solvent was distilled out to obtain 0.35 g of 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-thiophenecarboxylic acid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:

3.82 (s, 3H), 3.85 (s, 3H), 6.86 (m, 2H, AA'BB'),  
6.92 (m, 2H, AA'BB'), 7.12 (s, 1H), 7.18 (m, 2H, AA'BB'),  
7.31 (m, 2H, AA'BB'), 7.87 (d, J=4.0Hz, 1H), 8.43 (d, J=4.0Hz, 1H)

#### Example 155

Methyl (±)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-thiophenecarboxylate



0.5 g (1.15 mmol) of 5-[1,5-bis(4-methoxyphenyl)pyrazol-3-ylcarbonyl]-2-thiophenecarboxylic acid was dispersed in 10 ml of methanol and 2 ml of water. Thereto was added 160 mg (4.2 mmol) of sodium borohydride. It was stirred at room temperature for 3 hours. Thereto was added 10 ml of acetone and 1 ml of acetic acid. It was extracted with ethyl acetate. The extract was dried with magnesium sulfate and filtered. The solvent was distilled out to obtain the residue, to which was added 5 ml of dimethylformamide to obtain solution and then 120 mg (3 mmol) of 60% sodium hydride. To the reaction mixture was added dropwise 0.5 ml (7.7 mmol) of methyl iodide. It was stirred at room temperature for 30 minutes. Thereto was added water and it was extracted with ethyl acetate. The organic phase was washed with saturated solution of sodium chloride and dried with magnesium sulfate. The solvent was distilled out to obtain the residue, which was purified with silicagel column chromatography eluting with n-hexane-ethyl acetate to obtain 360 mg of methyl ( $\pm$ )-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-

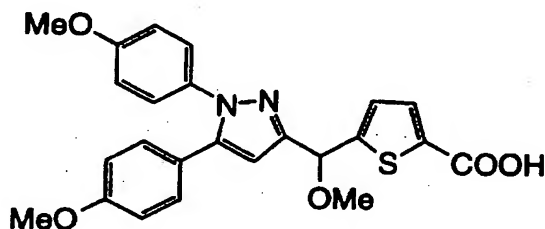
yl]-1-methoxymethyl]-2-thiophenecarboxylate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:

3.49 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 5.30 (s, 1H),  
6.45 (s, 1H), 6.80 (m, 2H, AA'BB'), 6.85 (m, 2H, AA'BB'),  
7.06 (d, J=4.0Hz, 1H), 7.12 (m, 2H, AA'BB'),  
7.22 (m, 2H, AA'BB'), 7.68 (d, J=4.0Hz, 1H)

#### Example 156

(±)-5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-thiophenecarboxylic acid



To 360 mg (0.78 mmol) of methyl (±)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-thiophenecarboxylate was added 4 ml of methanol, 0.5 ml of water and 0.4 ml of 5N solution of sodium hydroxide. The mixture was stirred at 65 °C for 30 minutes. The reaction mixture was diluted with water and citric acid was added thereto to render it acidic. It was extracted with ethyl acetate. The organic phase was

washed with saturated solution of sodium chloride and dried with magnesium sulfate. Having been filtered, the solvent was distilled out to obtain the residue, to which was added small amount of n-hexane to crystallize it. The crystals were filtered and dried to obtain 270 mg of colorless crystals of (±)-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-thiophenecarboxylic acid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>)δ:

3.50 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 5.68 (s, 1H), 6.45 (s, 1H),  
6.80 (m, 2H, AA'BB'), 6.86 (m, 2H, AA'BB'), 7.09 (d, J=3.5Hz, 1H),  
7.12 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'),  
7.75 (d, J=3.5Hz, 1H)

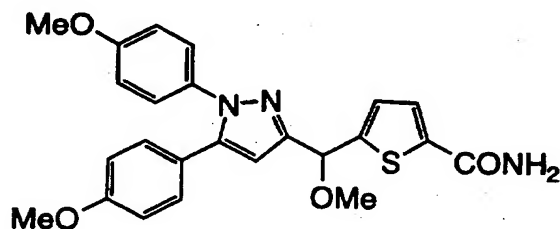
The compounds shown in Table 25 were obtained in the same manner as that of Example 156.

Table 25

Ex.no.	Chemical formula	NMR data
157		NMR (CDCl <sub>3</sub> ) δ 3.51 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 5.56 (s, 1H), 6.36 (s, 1H), 6.80 (m, 2H, <u>AA'</u> <u>BB'</u> ), 6.85 (m, 2H, <u>AA'</u> <u>BB'</u> ), 7.11 (m, 2H, <u>AA'</u> <u>BB'</u> ), 7.22 (m, 2H, <u>AA'</u> <u>BB'</u> ), 8.53 (bs, 1H), 8.96 (bs, 1H), 9.21 (bs, 1H)
158		NMR (CDCl <sub>3</sub> ) δ 3.49 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 5.55 (s, 1H), 6.55 (s, 1H), 6.57 (d, J=3.5Hz, 1H), 6.81 (m, 2H, <u>AA'</u> <u>BB'</u> ), 6.85 (m, 2H, <u>AA'</u> <u>BB'</u> ), 7.14 (m, 2H, <u>AA'</u> <u>BB'</u> ), 7.22 (m, 2H, <u>AA'</u> <u>BB'</u> ), 7.27 (d, J=3.5Hz, 1H)

### Example 159

(±)-5-[1-[1.5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl-2-thiophenecarboxamide



180 mg (0.4 mmol) of ( $\pm$ )-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl]-2-

thiophenecarboxylic acid was dissolved in 2 ml of dimethylformamide. Thereto was added 68 mg (0.5 mmol) of 1-hydroxybenzotriazol and 71 mg (0.46 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was stirred at room temperature for 3 hours. Thereinto was blown ammonia gas at room temperature for 5 minutes. It was stirred at room temperature for 1.5 hours. 30 ml of water was added thereto and it was extracted with ethyl acetate. The organic phase was washed with saturated aqueous solution of sodium bicarbonate and dried with magnesium sulfate. Having been filtered, the solvent was distilled out to obtain the residue, which was treated with column chromatography using silicagel NAM200H eluting with methanol-dichloromethane, to obtain 57 mg of white, amorphous powder, ( $\pm$ )-5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1-methoxymethyl-2-thiophenecarboxamide

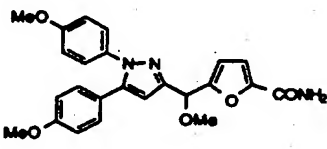
$^1\text{H-NMR}(\text{CDCl}_3)\delta$ :

3.48 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 5.65 (s, 1H), 5.85 (bs, 2H),  
6.46 (s, 1H), 6.79 (m, 2H, AA'BB'), 6.85 (m, 2H, AA'BB'),  
7.05 (d, J=4.0Hz, 1H), 7.12 (m, 2H, AA'BB'), 7.21 (m, 2H, AA'BB'),  
7.42 (d, J=4.0Hz, 1H)

The compound shown in Table 26 was obtained in the same

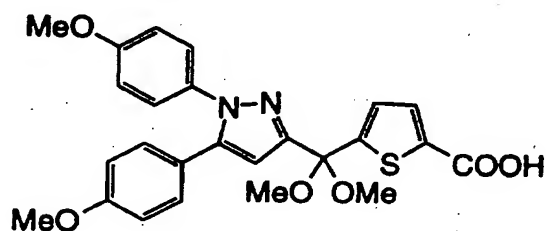
manner as that of Example 159.

Table 26

Ex.no.	Chemical formula	NMR data
160		NMR(CDCl <sub>3</sub> ) $\delta$ 3.47(s, 3H), 3.79(s, 3H), 3.80(s, 3H), 5.49(s, 1H), 5.77(bs, 1H), 6.42(bs, 1H), 6.49(s, 1H), 6.53(d, J=3.0Hz, 1H), 6.81(m, 2H, AA'BB'), 6.85(m, 2H, AA'BB'), 7.12-7.14(m, 3H), 7.21(m, 2H, AA'BB')

Example 161

5-[1-[1,5-Bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-thiophenecarboxylic acid



1.0 g (2.3 mmol) of 1,5-bis(4-methoxyphenyl)pyrazol-3-yl thiophenyl ketone dimethyl acetal was dissolved in 30 ml of anhydrous tetrahydrofuran. 0.52 ml of N,N,N',N'-tetramethylethylenediamine was added thereto. The mixture was stirred at minus 78 °C under nitrogen gas. Thereto was added 2.1 ml (3.36 mmol) of 1.6 M solution of n-butyllithium in n-



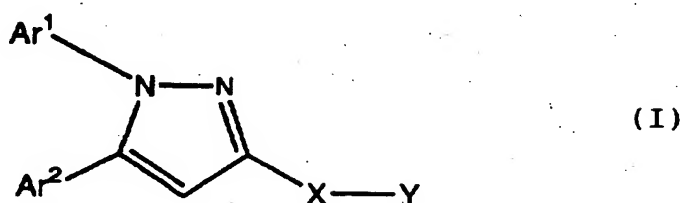
hexane. The reaction mixture was treated with 50 g of dry ice and heated gradually up to zero °C. Thereto was added water and solution of sodium hydroxide to render it strongly alkaline. It was washed with ether. To the aqueous phase was added citric acid to render it acidic. It was extracted with ethyl acetate. The organic phase was washed with saturated aqueous solution of sodium chloride and dried with magnesium sulfate. Having been filtered, the solvent was distilled out to obtain the residue, which was purified with silicagel column chromatography eluting with methanol-dichloromethane, to obtain 110 mg of white crystals, 5-[1-[1,5-bis(4-methoxyphenyl)pyrazol-3-yl]-1,1-dimethoxymethyl]-2-thiophenecarboxylic acid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:

3.34 (s, 6H), 3.79 (s, 3H), 3.80 (s, 3H), 6.44 (s, 1H),  
6.79 (m, 2H, AA'BB'), 6.82 (m, 2H, AA'BB'), 7.11 (m, 2H, AA'BB'),  
7.16 (d, J=4.0Hz, 1H), 7.21 (m, 2H, AA'BB'), 7.74 (d, J=4.0Hz, 1H)

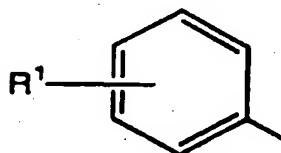
## CLAIMS

1. A pyrazole derivative represented by the following formula (I) or a physiologically acceptable salt thereof:



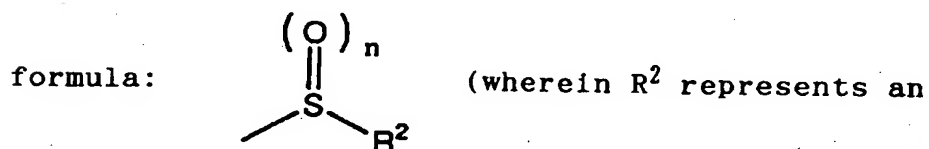
wherein Ar<sup>1</sup> and Ar<sup>2</sup> may be the same or different from each other and each represents an optionally substituted heterocyclic group or a group represented

by formula:



[wherein R<sup>1</sup>

represents a hydrogen atom, an optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, a halogen atom or a group represented by



optionally halogenated lower alkyl group or an

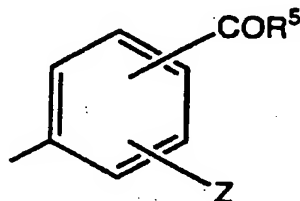
optionally substituted amino group; and n represents an integer of 0, 1 or 2)];

X represents a group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  may be the same or different from each other and each represents a hydrogen atom, a hydroxyl group, an optionally halogenated lower alkoxy group, a halogen atom or an optionally protected carboxyl group, or  $CR^3R^4$  may form a five- or six-membered ring having a carbon atom(s) optionally together with an oxygen atom(s) as the ring-constituting atoms); or a group represented by formula:  $>C=O$ ; and

Y represents an optionally substituted aryl group, an optionally substituted furyl group, an optionally substituted thienyl group, an optionally substituted pyridyl group, an optionally substituted thiazolyl group, an optionally substituted tetrazolyl group, an optionally halogenated lower alkyl group, an optionally halogenated lower alkenyl group, an optionally substituted arylalkyl group, an optionally substituted arylalkenyl group, an optionally substituted lower alkynyl group, an alkyl group substituted with an optionally protected carboxyl group or an alkenyl group substituted with an optionally protected carboxyl group when X represents

a group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  are each as defined above); or Y represents a group

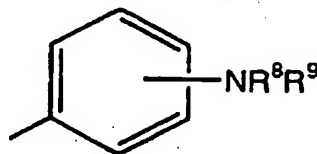
represented by formula:



[wherein  $R^5$

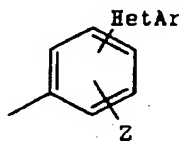
represents a hydroxyl group, an optionally halogenated lower alkoxy group, an arylalkoxy group or a group represented by formula:  $-NR^6R^7$  (wherein  $R^6$  and  $R^7$  may be the same or different from each other and each represents a hydrogen atom, an optionally halogenated lower alkyl group or an alkoxyalkyl group, or  $NR^6R^7$  may form a five- or six-membered heterocyclic ring having a carbon atom(s) and a nitrogen atom(s) optionally together with an oxygen atom(s) and/or a sulfur atom(s) as the ring-constituting atoms); and Z represents a hydrogen atom, an optionally halogenated lower alkyl group, an optionally halogenated lower alkoxy group, an alkylthio group, an alkylsulfonyl group, an alkylsulfoxide group or a halogen atom)], a

group represented by formula:



(wherein  $R^8$  and  $R^9$  may be the same or different from

each other and each represents a hydrogen atom, an alkylsulfonyl group, or an optionally halogenated lower alkyl group), a group represented by formula:

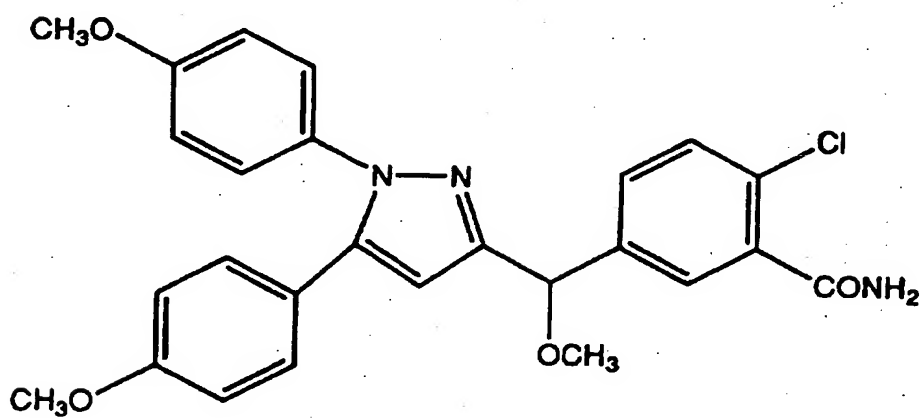
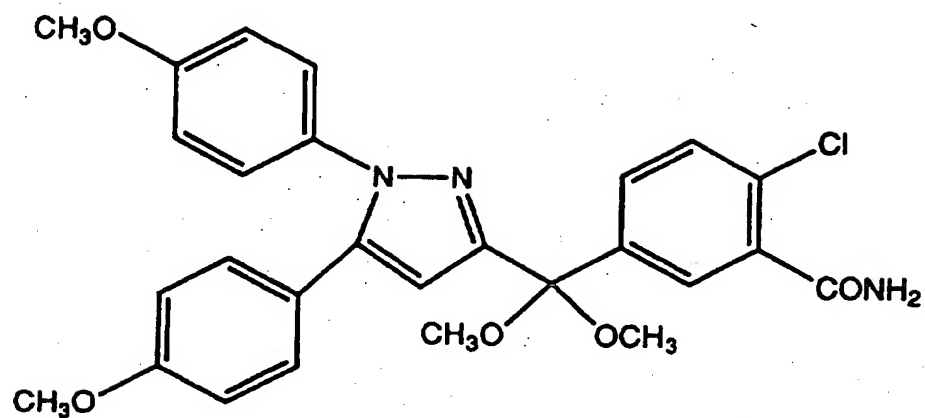


[wherein HetAr represents an optionally

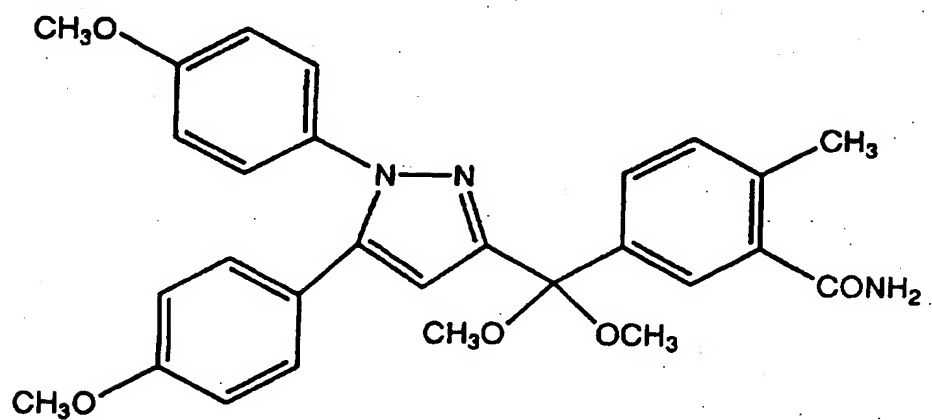
substituted five- or six-membered heterocyclic ring having a carbon atom(s) together with at least one of a nitrogen atom(s), an oxygen atom(s) and a sulfur atom(s) as the ring-constituting atoms; and Z is as defined above] or an optionally substituted thienyl group when X represents a group represented by formula:  $>C=O$ .

2. The pyrazole derivative or the physiologically acceptable salt thereof as set forth in Claim 1 wherein X is a group represented by formula:  $>CR^3R^4$  (wherein  $R^3$  and  $R^4$  are each as defined above) and Y is an optionally substituted phenyl group.

3. The pyrazole derivative or the physiologically acceptable salt thereof as set forth in Claim 1, which is a compound selected from the group consisting of



and



4. A pharmaceutical composition comprising the pyrazole derivative or the physiologically acceptable salt thereof as set forth in Claim 1, and a pharmacologically acceptable filler.

5. A use of the pyrazole derivative or the physiologically acceptable salt thereof as set forth in Claim 1 for preparing a medicament being effective in treatment of a disease to which the simultaneously suppression of the production of both of a prostaglandin(s) and a leukotriene(s) is effective.

6. The use as set forth in Claim 5, wherein the medicament is an antirheumatic or an anti-inflammatory/analgesic agent.

7. A method for preparing a medicament being effective in treatment of a disease to which the simultaneously suppression of the production of both of a prostaglandin(s) and a leukotriene(s) is effective, which comprises using the pyrazole derivative or the physiologically acceptable salt thereof as set forth in Claim 1 as the active ingredient.

8. The method as set forth in Claim 7, wherein the medicament is an antirheumatic or an anti-inflammatory/analgesic agent.

9. An antirheumatic comprising the pyrazole

derivative or the physiologically acceptable salt thereof as set forth in Claim 1 as the active ingredient.

10. An anti-inflammatory/analgesic agent comprising the pyrazole derivative or the physiologically acceptable salt thereof as set forth in Claim 1 as the active ingredient.



# INTERNATIONAL SEARCH REPORT

Inventor's Application No.  
PCT/JP 95/02250

## CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D231/12 A61K31/415 C07D401/06 C07D403/06 C07D403/10  
C07D403/12 C07D405/04 C07D405/06 C07D405/10 C07D409/04  
C07D409/06 C07D413/10 C07D417/06 C07D417/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP,A,0 293 220 (ORTHO PHARMACEUTICAL CORPORATION) 30 November 1988  see page 45 - page 46; claim 18  see page 24; example 26  see page 25; table 5  see page 26; table 6, compound no. 114  see page 34, line 10 - line 15  see page 34; table 13, compound no. 109  ---  -/--</p>	1, 2, 4-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

5 February 1996

Date of mailing of the international search report

16.02.96

Name and mailing address of the ISA

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Fink, D

## INTERNATIONAL SEARCH REPORT

 Int. Application No  
 PCT/JP 95/02250

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 248 594 (ORTHO PHARMACEUTICAL CORPORATION) 9 December 1987 see page 48 - page 49; claim 1 see page 15; table 2 see page 16; table 2 see page 18; table 2 see page 24 - page 25; table 3 see page 26; table 4 see page 31; table 5 see page 32 - page 34; tables 6-9 ---	1,4-10
X	EP,A,0 554 829 (FUJISAWA PHARMACEUTICAL CO., LTD.) 11 August 1993 see page 30; claim 1 ---	1,4-10
X	CHEMICAL ABSTRACTS, vol. 93, no. 7, 18 August 1980, Columbus, Ohio, US; abstract no. 70321z, T. AXENROD ET AL. 'Carbon-13 NMR: the stereochemical dependence of nitrogen-15-carbon-13 coupling constants in pyrazoles.' page 858 ;column 1 ; see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 10th Collective Index, vol. 86-95, 1977-1981, page 45479CS: RN [74441-34-2] & ORG. MAGN. RESON., vol.13, no.3, 1980 pages 197 - 199 ---	1,2
X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, no.23, 3 December 1969, LETCHWORTH GB pages 1393 - 1394 J.H. LEE ET AL. '2,3,5,6-Tetra-aryl-1,2,4, 5-tetra-azapentalenes. A New Heteroaromatic System' see page 1393, column 2, compound no. (VI) ---	1,2
P,X	WO,A,95 15316 (G.D. SEARLE & CO.) 8 June 1995 see page 184 - page 187; claim 1 see page 138 - page 139; example 174 see page 143; example 183; table VIII ---	1,4-10
P,X	WO,A,95 15315 (G.D. SEARLE & CO.) 8 June 1995 see page 19; claim 1 -----	1,4-10

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 95/02250

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Claims searched incompletely: 1, 4-10  
Please see attached sheet ./.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The novelty search on the compounds of general formula (I) revealed a vast amount of novelty-destroying compounds with respect to claim 1 of the present application.

Therefore, the search and the search report - as far as the novelty of the compounds of formula I is concerned - has been limited (for economical reasons; cf. WIPO: PCT Search Guidelines, 1992; Chapter III, item 2) to the compounds of claim 1 of the present application, wherein:

Y = an optionally substituted aryl group,  
or  
an optionally substituted hetaryl group  
(such as the furyl-, the thienyl-, the  
pyridyl-, the thiazolyl- or the tetrazolyl-  
group);

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. J. Application No  
PCT/JP 95/02250

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0293220	30-11-88	AT-T- 110717	15-09-94
		AU-B- 611437	13-06-91
		AU-B- 1657488	01-12-88
		CA-A- 1319149	15-06-93
		DE-D- 3851258	06-10-94
		DE-T- 3851258	15-12-94
		ES-T- 2058280	01-11-94
		JP-A- 1052758	28-02-89
		US-A- 5051518	24-09-91
EP-A-0248594	09-12-87	US-A- 4826868	02-05-89
		AU-B- 596844	17-05-90
		AU-B- 7360887	10-12-87
		CA-A- 1337122	26-09-95
		CN-B- 1028227	19-04-95
		DE-D- 3788244	05-01-94
		DE-T- 3788244	14-04-94
		DK-B- 170202	12-06-95
		ES-T- 2059377	16-11-94
		FI-B- 94340	15-05-95
		HU-A- 68247	28-06-95
		SG-A- 3294	15-04-94
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